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THE PULSE FLOW IN THE BRACHIAL ARTERY

V. THE INFLUENCE OF CERTAIN DRUGS *

ALBION WALTER HEWLETT, M.D.

SAN FRANCISCO

GENERAL CONSIDERATIONS

By methods which have been described elsewhere[1] we are able to determine (*a*) the average blood flow in the arm of man over brief periods of time, (*b*) the volume and form of the pulse wave entering the arm, and (*c*) the blood flow in the main arm arteries during each portion of the pulse cycle. The last, which we have called the pulse flow in the brachial artery, may be recorded directly. It is, however, a resultant of the two preceding components; that is, of the average blood flow and of the variations in this flow produced by the entrance of the pulse wave into the arm.

The average rate of blood flow in the arm depends in part on the average blood pressure, and in part on the local resistance opposed to the flow of blood through the smaller arteries and capillaries of the arm. By the method which we have used this average blood flow varies considerably even in a single individual, apparently because the body temperature is being constantly regulated by alterations in the rate of blood flow through its peripheral tissues. Even when we have made some effort to maintain a relatively constant external temperature we have at times encountered gradual changes in the rate of arm circulation. For this reason we have not been able to draw conclusions as to the effect of drugs on this rate unless the changes observed were marked and constant.[2]

* Submitted for publication Feb. 1, 1917.

* From the Department of Internal Medicine, University of Michigan.

1. Hewlett, A. W., and van Zwaluwenburg, J. G.: The Pulse Flow in the Brachial Artery. I. Technic and General Considerations, THE ARCHIVES INT. MED., 1913, **12**, 1.

2. G. N. Stewart (Studies on the Circulation in Man. I. The Measurement of the Blood Flow in the Hands, Heart, 1911, **3**, 33) found, on the contrary, a rather constant rate of blood flow through the hand for any given individual. In the method which he used the hand is immersed in water of a relatively constant temperature. Possibly this may exercise a steadying influence on the local blood flow.

The volume and form of the pulse wave entering the arm depend on a complex interaction of many factors. Among these are the size and duration of the ventricular output and the condition of the large and small arteries, not only in the arm itself, but in important vascular areas elsewhere. An adequate physical explanation of changes in the volume and form of the pulse does not seem possible at the present time. In the present paper, therefore, I propose merely to record some observations in which the pulse flow in the arm was determined before and after the administration of certain drugs in therapeutic doses.

Nitroglycerin.—The changes which follow the placing of one or two drops of a 1 per cent. solution of nitroglycerin on the tongue have been described in a previous paper.[3] These consist of: (1) a swelling of the arm; (2) an increase in the size of the volume pulse; (3) a change toward a more pointed or collapsing pulse; (4) the disappearance of the smaller secondary waves, and (5) no marked or constant alteration in the rate of blood flow through the arm. These typical pulse changes usually begin in two or three minutes, reach their maximum in five or six minutes and pass off in about fifteen minutes. A considerable number of observations, fifty or more, have shown the constancy of these changes in normal young adults. In chronic arterial hypertension, similar changes may also be produced, although not so readily as in young adults. It is noteworthy that the pulse changes in such patients may occur, even when the blood pressure, though reduced, is still far above the normal.

Inasmuch as it seemed probable that these changes might be due in part to a reduction in the elastic coefficient of the larger arm arteries, and that such a reduction might be accompanied by a slower propagation of the arterial pulse wave in the arm, the difference in time between the onset of the subclavian and radial pulses before and during the typical nitroglycerin action was determined in eleven experiments. In four of these the propagation of the pulse wave became somewhat slower, while in the remaining seven no definite alteration in the rate of propagation could be demonstrated. It seems evident, therefore, that the typical changes in the pulse may occur without a demonstrable alteration in the rate of pulse propagation from the neck to the wrist.

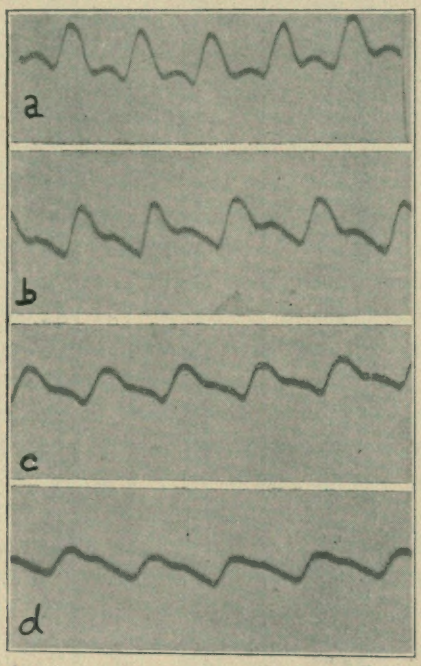
In a previous paper[3] it was pointed out that the changes induced by nitroglycerin are more evident in the volume pulse of the arm than in the pulse recorded by placing a tambour over the carotid or sub-

3. Hewlett, A. W., van Zwaluwenburg, J. G., and Agnew, J. H.: The Pulse Flow in the Brachial Artery. II. Relation to the Average Blood Flow. Effect of Nitroglycerin, THE ARCHIVES INT. MED., 1913, **12**, 13.

clavian arteries. Changes in the latter do occur, however, and subsequent records have shown that in some instances they are quite striking. One must therefore attribute the alteration in the arm pulse not only to local vascular changes, but also, in part, either to an alteration in the cardiac output or to changes in the vessels elsewhere in the body.

Electrocardiograms were made on several occasions before and during the nitroglycerin effect, but no noteworthy changes in form were noted.

Pituitary Extract.—It is well known that injections into animals of extracts prepared from the posterior lobe or from the pars intermedia



Curves showing alterations in the febrile pulse produced by the injection of 1.5 c.c. of pituitary extract (from Patient 2 (Sw.) of Table 1). *a*. Before the injection; *b*. seventeen minutes after the injection; *c*. twenty-two minutes after the injection; *d*. fifty minutes after the injection. Note that the volume pulse diminished in size and that its form changed from the pointed or collapsing type, often seen in fevers, to a sustained type.

of the pituitary gland, produce an arterial constriction with a rise of blood pressure. The effect of therapeutic doses on the blood pressure of certain patients was studied in this clinic by Dr. H. B. Schmidt, who found that while the systolic pressure was not altered in any constant manner, there was, as a rule, a moderate rise in the diastolic pressure.

TABLE 1.—Effect of Pituitary Extract on Pulse Form in Patients Showing a Pointed Type of Pulse

Case	Diagnosis	Time with Reference to Pit. Extr.	Pulse Rate	Volume of Pulse Wave, c.c.	Blood Flow in Arm	Pointed Quality
1. Sw.	Tuberculosis	Before	118	0.8	....	+ + + +
		Before	113	0.7	....	+ + +
		Before	109	0.8	....	+ + + +
		Before	108	0.7	....	+ + +
		5 min. after 1.5 c.c.	118	0.6	....	+ + +
		10 min.	114	0.6	....	+ + +
		18 min.	107	0.6	....	+ + +
		30 min.	98	0.5	....	+
		38 min.	97	0.5	....	+
2. Sw.	Tuberculosis	Before	108	0.33	....	+ + + +
		Before	112	0.34	1.6	+ + + +
		2 min. after 1.5 c.c.	100	0.37	2.4	+ + +
		4 min.	90	0.33	1.9	+ +
		6 min.	96	0.33	1.9	+ + +
		8 min.	104	0.33	1.7	+ + +
		13 min.	140	0.46	12.0	+ + +
		15 min.	111	0.30	4.3	+ + +
		17 min.	106	0.29	1.9	+
		22 min.	104	0.26	2.7	+
		25 min.	96	0.26	2.0	—
		35 min.	96	0.26	1.9	—
		40 min.	95	0.26	2.4	—
		50 min.	92	0.24	2.2	—
3. O. H.	Tuberculosis	Before	75	0.5	3.0	+ + +
		Before	80	0.5	2.5	+ + +
		3 min. after 1.5 c.c.	73	0.45	2.6	+ + +
		8 min.	74	0.45	2.5	+ + +
		10 min.	77	0.4	4.5	+ + +
		11 min.	73	0.45	4.5	+ +
		15 min.	76	0.45	2.0	+ +
		20 min.	80	0.45	2.4	+
		25 min.	80	0.4	2.8	+
		30 min.	82	0.4	....	+
		35 min.	75	0.35	2.4	—
		40 min.	74	0.3	....	+
		50 min.	75	0.3	1.2	—
		55 min.	70	0.3	2.0	—
4. C.	Fever	Before	117	0.5	4.0	+ + +
		Before	117	0.45	3.4	+ + +
		3 min. after 1.5 c.c.	115	0.43	3.0	+ +
		6 min.	115	0.35	3.0	+
		9 min.	117	0.4	5.0	—
		14 min.	119	0.4	6.0	—
		22 min.	112	0.4	....	—
		32 min.	120	0.35	6.7	—
5. K.	Fever	Before	65	0.5	....	+ +
		Before	66	0.5	....	+ +
		14 min. after 1.5 c.c.	66	0.45	....	+
		16 min.	64	0.4	....	+
		20 min.	70	0.35	....	—
6. H.	Tuberculosis	Before	98	0.6	7.5	+ + +
		Before	100	0.6	7.5	+ + +
		Before	102	0.6	6.5	+ + +
		3 min. after 1.5 c.c.	100	0.6	6.8	+ +
		7 min.	98	0.6	8.0	+ + +
		10 min.	97	0.6	8.0	+ +
		14 min.	102	0.6	9.0	+ +
		32 min.	103	0.5	7.3	+ +
		34 min.	104	0.6	9.0	+ +
		42 min.	97	0.5	7.2	+ +
		55 min.	100	0.5	7.0	+ +
7. A.	Tuberculosis	Before	122	0.4	2.0	+ + + +
		Before	121	0.4	1.9	+ + + +
		5 min. after 1 c.c.	117	0.4	2.0	+ + + +
		10 min.	115	0.4	2.0	+ + + +
		20 min.	117	0.4	2.4	+ + + +
		30 min.	117	0.4	3.0	+ + + +
8. L.	Aortic insufficiency	Before	88	1.5	5.0	+ + +
		Before	94	1.4	....	+ + +
		5 min. after 1 c.c.	84	1.3	....	+ +
		7 min.	85	1.3	4.0	+ +
		10 min.	84	1.3	10.0	+
		17 min.	87	1.2	12.0	+
		22 min.	88	1.3	8.0	+ +

We have shown elsewhere[4] that in many fevers, and particularly in typhoid fever and in febrile tuberculosis, the pulse form resembles that produced by nitroglycerin, but that its size is on the average smaller than normal. We have gained the impression, furthermore, that as the circulation shows evidence of failure during infections, the pulse becomes progressively smaller. The effect of pituitary extracts on this type of pulse was studied with the hope that some basis might be furnished for the use of such extracts during the circulatory failure which may complicate severe infections.

The effects that were observed after the intramuscular injection of pituitary extract[5] are shown in Table 1 and in Figure 1. When striking changes occurred they consisted of: (1) a decrease in the size of the volume pulse; (2) a change from a pointed to a more sustained pulse, and (3) some tendency for a transient increase in the blood flow through the arm, which increase was not definitely related to the change in pulse form and volume. The alterations in pulse volume and form usually became evident in from five to ten minutes after the injection of the pituitary extract, and they persisted for thirty to fifty minutes or more. The onset and duration of this action on the pulse corresponds to the onset and duration of the effects on uterine contractions during labor, for Quigley[6] asserts that these latter appear in three to ten minutes and last from sixty to ninety minutes.

In six of the eight observations here recorded the changes in the pulse produced by the pituitary extract were marked; in one they were indicated, while in one, in which 1 c.c. only was injected, they were absent. A considerable number of other pituitary extract injections were given without making a series of records. In some of these the above effects on the pulse were confirmed by a few records, while in still others the change to a smaller and more sustained radial pulse was noted on palpation of the radial artery. The carotid or subclavian pulse was recorded in a few instances and a similar tendency toward a more sustained form under the influence of pituitary substance was noted.

It seems certain, therefore, that pituitary extract in rather large doses produces a definite and fairly constant alteration in the size and form of the volume pulse recorded from the arm of febrile patients. This alteration is almost the opposite of that produced by nitroglycerin.

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4. Hewlett, A. W.: The Pulse Flow in the Brachial Artery. IV. Reflections of the Primary Wave in Dicrotic and Monocrotic Pulse Forms, THE ARCHIVES INT. MED., 1914, **15,** 609.

5. The preparation of Parke, Davis & Co. (pituitrin) was injected intramuscularly, usually in doses of 1.5 c.c.

6. Quigley, J. K.: Pituitrin in Obstetrics, New York State Med. Jour., 1913, **13,** 317.

On account of this contrast, as well as on account of the known effect of pituitary extracts on animals, it seems highly probable that the changes observed in patients were due to arterial constriction. In our opinion, however, such a constriction is not likely to prove of great value in combating the circulatory failure during infections. In the first place, the volume pulse is usually quite small during such collapse, and pituitary extract, though restoring the normal form, makes the volume still smaller. In the second place, it seems probable that this type of circulatory failure is not due primarily to arterial relaxation, but to a deficient blood supply to the heart, owing perhaps to a stagnation of blood in the abdominal capillaries and veins. We have no evidence that pituitary extract will influence such a disturbance in the blood supply to the heart.

Veratrum Viride.—The effect of veratrum album on the pulse rate and the blood pressure of man has been recently studied by Collins,[7] who found that large therapeutic doses reduce both the pulse rate and the blood pressure, and that these reductions may occur in certain cases without unpleasant gastro-intestinal symptoms. We have repeated these observations, using the hospital tincture or the fluid extract of veratrum viride, and were able to confirm Collins' observations. The effective dose, however, was considerably larger than that used by Collins, and it is evident that some method of standardization will be necessary if veratrum is to be employed in general practice.

Like Collins, we found that in some patients with chronic arterial hypertension, extraordinary reductions of the blood pressure can be produced by this drug. In one patient, for example, the systolic pressure fell from over 200 to 108 mm. in the course of a few hours Other patients with normal as well as with increased blood pressure proved more resistant to the drug, and in one instance vomiting occurred at a time when no reduction of blood pressure had taken place. It is noteworthy, however, that the reduction in blood pressure may occur with none of the disagreeable symptoms which usually accompany a similar reduction after large doses of the nitrites. In several patients with chronic hypertension the tincture of veratrum viride was continued for several days in doses of 30 or more minims three or four times a day with no unpleasant symptoms, and with a slight but not very definite reduction in pressure.

In eight instances the pulse flow in the arm was recorded before and during the administration of veratrum viride. These records (Table 2) show that the fall in blood pressure produced by this drug is not accompanied by the changes in pulse size or form which char-

7. Collins, R. J.: The Clinical Actions of Veratrum, THE ARCHIVES INT. MED., 1915, **16,** 54.

acterize the action of effective doses of nitroglycerin. It will be recalled that the latter cause an increase in the size of the volume pulse in the arm and that they tend to produce a pointed pulse. When veratrum viride is given in effective doses there may be a slight increase in the volume of the individual pulse waves, but this is not constant; nor is the form of the pulse wave materially altered. When changes in

TABLE 2.—EFFECTS OF VERATRUM VIRIDE

Case	Dose of Tincture, Minims	Blood Pressure	Pulse Rate	Volume of Pulse Wave, c.c.	Blood Flow in Arm	Pointed Quality
1. Kn.	Before	242-140	78	0.45	0.86	++
	After 90	210-122	60	0.52	1.0	+
2. Sm.	Before	166-106	92	0.42	1.7	—
	After 160	130-60	74	0.60	1.7	—
	Followed by Atropin 1/60 gr.	130-88	90	0.37	2.1	+
3. Sm.	Before	200-126	102	0.60	.....	—
	After 120	122-70	70	0.58	Increased	—
4. Ja.	Before	.....	112	0.76	.....	++
	After	.....	95	0.70	.....	++
5. Ja.	Before	126-72	96	0.60	.....	+
	After 140	126-70	96	0.78	.....	+
6. McG.	Before	186-105	99	1.08	.....	—
	After 200	183-110	100	1.2	.....	++
7. In.	Before	260-132	84	....	.....	+
	After	186-100	60	....	.....	+
8. Ga.	Before	220-112	87	1.3	.....	++
	After	204-103	60	1.3	Increased	—

TABLE 3.—EFFECT OF ATROPIN ON ARM PULSE*

No.	Time	Pulse Rate	Volume of Pulse Wave, c.c.	Blood Flow in Arm	Pointed Quality
1	After	66	0.4	4.0	—
	Before	73	0.3	3.5	+
2	Before	75	0.3	1.3	+
	After	85	0.3	1.7	++
3	Before	61	0.6	1.7	+
	After	82	0.5	3.4	++
4	Before	76	0.4	1.4	—
	After	80	0.5	2.0	—
5	Before	60	0.7	.....	—
	After	62	0.6	Increased	—
6	Before	100	0.3	2.0	++
	After	140	0.4	3.8	++++

* Records taken before and about half an hour after the injection of 1/50 gr. atropin sulphate.

form did occur, the collapsing quality was more frequently lessened than increased. These slight alterations in the direction of a larger and more sustained pulse may in all probability be attributed to the slower pulse rate rather than to any change in the arteries.

Atropin.—On six occasions atropin sulphate was injected subcutaneously in doses of $\frac{1}{50}$ grain, and the effect on the pulse flow was

recorded at the end of about half an hour. The subjects of these observations were normal so far as the cardiovascular apparatus was concerned. As may be seen from Table 3, the pulse rate was somewhat accelerated in four instances, considerably accelerated in one, and unaffected in one. The size of the volume pulse in the arm was not materially altered. The rate of blood flow was somewhat accelerated in five instances and diminished in one. The pulse form became slightly more pointed in four instances, and it is noteworthy that this change occurred in those cases which showed the more marked acceleration in the pulse rate.

Negative Results.—Records made after the injection of a number of other remedies which are believed to act on the cardiovascular apparatus showed no definite or marked effect on the pulse flow.

In seven patients the pulse flow was determined before and after the intravenous injection of strophanthin. In six patients who had a normal sinus rhythm, no striking changes were observed. Two of these had the typical pointed pulse of fever, while two others were suffering from mild grades of cardiac decompensation. The seventh patient, who showed auriculr fibrillation and a rapid and irregular pulse, reacted with the usual slowing of the ventricular rate. This was accompanied by an increase in the size of the individual pulse waves.

Camphor dissolved in oil, in doses of from 5 to 10 grains, was injected subcutaneously into five patients, three of whom showed a pointed febrile pulse. No noteworthy alterations either in the pulse size or form were noted.

Pulse records were made in two patients who received subcutaneous injections of epinephrin solution for the relief of asthmatic attacks. One received 8 and the other 15 minims of Parke, Davis and Company's 1 to 1,000 solution. Although the paroxysms of asthma were relieved, no effect on the pulse form was observed.

Finally, a number of injections of strychnin sulphate were given in doses of $\frac{1}{20}$ to $\frac{1}{10}$ grain without any definite effect on the size or form of the pulse waves. In some of these cases, however, there appeared to be an increase in the rate of blood flow in the arm, which became most evident about half an hour after the injection.

CONCLUSIONS

Of the drugs studied, nitroglycerin, pituitary extract, veratrum viride, atropin, strophanthin, camphor, epinephrin and strychnin, only the first two produced definite and unmistakable alterations in the size and form of the volume pulse recorded from the arm of man. Nitro-

glycerin caused the pulse to become larger and more pointed, while pituitary extract had the opposite effect.

The fall of pressure produced by adequate doses of veratrum viride is not accompanied by definite changes in the pulse form. In this respect the action of this drug differs essentially from the action of nitroglycerin.

Lane Hospital.

STUDY OF A CASE OF DIABETES INSIPIDUS WITH SPECIAL REFERENCE TO THE MECHANISM OF THE DIURESIS AND OF THE ACTION OF PITUITARY EXTRACT ON IT*

C. D. CHRISTIE, M.D., AND G. N. STEWART, M.D.
CLEVELAND

The case of diabetes insipidus reported in this paper presented, on account of the high degree of the diuresis, an unusually good opportunity for the study of certain points in connection with the mechanism of the diuresis and the influence on it of extracts of the posterior lobe of the pituitary body. Although it was not possible to induce the patient to remain long enough in the hospital to enable us to complete our program, the results obtained seem worthy of being recorded.

The manner in which the excretion of water by the kidney is regulated has formed the subject of recent papers by Priestley[1] and by Haldane and Priestley.[2] They find, as T. M. Wilson,[3] working under the direction of one of us, previously showed, that the drinking of water is followed by a small diminution of the specific conductivity of the blood serum. According to Wilson, the meaning of this would seem to be that "when the relative volume of serum is increased (e. g., by drinking water) the serum becomes more dilute as regards salts, and therefore has a diminished specific conductivity. When the serum diminishes in amount, water seems to pass out of it in greater proportion than salts." Haldane and Priestley were unable to demonstrate any change in the relative volume of the plasma which could be detected by estimating the percentage hemoglobin content.[4] But Wilson, using a more delicate test, the determination of the relative volume of corpuscles and plasma by the electrical method,[5] was able to show that coincident with the decrease in the conductivity of the serum there was a slight increase in its volume as compared with that of the corpuscles.

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* Submitted for publication Feb. 15, 1917.

* From the Department of Medicine of Lakeside Hospital and the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

1. Priestley: Jour. Physiol., 1916, **50,** 304.
2. Haldane and Priestley: Jour. Physiol., 1916, **50,** 296.
3. Wilson, T. M.: Am. Jour. Physiol., 1905, **13,** 150.
4. Hemoglobin estimations and blood counts carried on throughout the period of observation on our patient failed to show any definite correspondence with the intake of water or the diuresis.
5. Stewart, G. N.: Jour. Physiol., 1899, **24,** 356.

It seemed to us not unlikely that during the great and abrupt changes in the diuresis produced in our case by posterior lobe extract, or by withholding water, or allowing it in the enormous amounts habitually taken by the patient, a greater and therefore more easily detectable effect might be produced on the blood than was possible in any normal individual.

An attempt was made by measuring the blood flow through the hands to determine whether posterior lobe extract produced any effect on the superficial vessels which might afford support to the view that it affects the diuresis by a change of caliber of the renal vessels.

The ability of the kidney to excrete a concentrated urine, and its behavior to so-called "functional tests," were also investigated.

An attempt to review the theories which have at various times been held in regard to the mechanism of diabetes insipidus would be out of place. It will suffice for our purpose to refer to a few of the investigations which have seemed to connect the condition with a change in the activity of the pituitary body.

The frequent association of diabetes insipidus with tumors and injuries about the base of the brain, and the demonstration by Claude Bernard that puncture of the floor of the fourth ventricle occasionally produced a polyuria without glycosuria, led many observers to the belief that the disease was in some way dependent on the central nervous system. Magnus and Schäfer[6] demonstrated that extracts of the hypophysis caused an increased urine output. Schäfer and Herring[7] showed the diuretic effect of hypophyseal extract to be a property of the pars intermedia. They claimed the diuretic action was due to a direct stimulation of the kidney cells, associated with local dilatation of the kidney vessels. The work of Schäfer and Herring has been pretty generally accepted. These observations suggested that diabetes insipidus might be a manifestation of a hyperactive pituitary body.

Cushing[8] later pointed out that patients and animals frequently developed a diuresis following the removal of the posterior lobe of the pituitary body which was not unlike diabetes insipidus. Frank[9] observed a patient in whom diabetes insipidus had developed coincidently with the lodgment in the sella turcica of a bullet which encroached on the posterior lobe of the pituitary body. Lewis and Mathews[10] produced an analogous condition in dogs by inserting foreign material in the sella which encroached on the pituitary body. Such observations cast doubt on the conception that diabetes insipidus was the result of an overfunctioning posterior lobe. Cushing,[8] von den Velden and Farmi[11] expressed the view that diabetes insipidus was the result of an underfunctioning pituitary body.

There are in the literature a number of instances of patients suffering from diabetes insipidus who have experienced amelioration in the symptoms after intramuscular injection of posterior lobe extract. Recently recorded instances

6. Magnus and Schäfer: Jour. Physiol., 1901-1902, **27,** 9 (Proc. Physiol. Soc.).
7. Schäfer and Herring: Phil. Tr. Roy. Soc., 1906, **199,** B. p. 1.
8. Cushing: The Pituitary Body and Its Disorders, 1912.
9. Frank: Berl. klin. Wchnschr., 1912, **49,** 393.
10. Lewis and Mathews: The Archives Int. Med., 1915, **15,** 451.
11. Von den Velden and Farmi: Berl. klin. Wchnschr., 1913, **50,** 2083.

are those of Motzfeldt[12] and Eisner.[13] Motzfeldt reported three cases in which the urine output was cut down markedly, and in one of the patients there had been almost complete relief from the symptoms by the administration of the fresh posterior portion of the gland by mouth.

REPORT OF CASE

History.—C. F., woman, single, aged 31, was admitted to the Lakeside Hospital medical service, Nov. 13, 1916.

The patient's health had always been good until the present trouble began. There was no history of acquired or congenital syphilis. She was well and working regularly four years prior to admission, when she noticed rather suddenly that she was passing larger quantities of urine than usual and that her thirst was unquenchable. She was forced to give up her work within a short time. She gradually became very weak, but did not lose weight. Since that time her condition has remained much the same. Some days the urine output and the thirst have been greater than on other days. The urine output, as near as we could determine from the history, has ranged from 8 to 16 liters daily. During this time she has had several attacks in which she would be confined to bed with shortness of breath and swollen legs. She has also suffered intensely with a "breaking out" on the hands and arms, worse in winter, when the pain and itching are almost intolerable.

Physical Examination.—If it were not for an anemia the patient would appear in robust health. She is well developed and slightly inclined toward adiposity. The skin was extremely dry and showed a high grade of anemia. On the dorsum of the forearms and hands there was a papulosquamous eruption. The skin in these areas was extremely rough and dry, with multiple fissures. There was some slight oozing in spots, with scab formation (dermatitis hiemalis). The examination of the eyes, pupils and eyegrounds was entirely negative. There was a venous hum; no thyroid enlargement. The examination of the chest was negative, aside from rather extreme cardiac enlargement. No murmurs or adventitious sounds were heard over the precordium. The pulse was regular and there was no elevation of blood pressure. There was a moderate increase in the volume of the liver, but it was not tender. Examination of the nervous system revealed no abnormal findings.

The urine was pale, of large quantity, and low specific gravity. There was a faint trace of albumin in the admission specimen, but subsequent examinations revealed none. There were no casts.

The blood showed: hemoglobin (Sahli), 35 per cent.; white blood cells, 7,800; red blood cells, 3,700,000.

Lumbar puncture revealed no increase in pressure; fluid normal in appearance; two cells per cubic centimeter. The Noguchi and Wassermann tests were negative.

Roentgenograms of the region about the sella turcica showed no increase in the size.

One sugar determination was made on the blood of this patient by the method of Lewis and Benedict. It was found to be 0.168 gm. per hundred c.c. This would represent a distinct hyperglycemia, but the patient had never shown sugar in the urine, so immediately following the above determination she was given 250 gm. of dextrose by mouth and subsequent urine specimens were examined for sugar. They were all negative. The reduction in the blood was probably not due to sugar.

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12. Motzfeldt: Boston Med. and Surg. Jour., 1916, **174,** 644.
13. Eisner: Deutsch. Arch. f. klin. Med., 1916, **120,** 438.

METHODS OF STUDY

Considerable difficulty was encountered in the management of this case. The patient frequently drank 2 liters of water at a time and voided a similar amount of urine. Strict supervision was required. She was placed in a room by herself and was constantly watched by a nurse. Four nurses were engaged in her care. Water was measured into flasks in the laboratory and delivered to the room as they were needed. Other fluids were measured and figured in with the intake. Food was given to the patient at 8 a. m., 12 m., and 5 p. m., no food being allowed between meals. The diet was general except on days indicated in Figure 1 on which water was restricted. On these days the regular Mosenthal renal test diet was given. The days when the renal test diet was being taken, 1,000 c.c. of water was given with each meal instead of the stipulated amount. No water was allowed between meals and no particular attempt was made to limit the water after 8 p. m. on these days. The weight was obtained at 8 a. m. without permitting the patient to drink or to void after 7 a. m.

Blood specimens were always taken from the median cephalic vein into a small amount of oxalate, for blood ureas, sugar, etc. For hematocrit and electrical conductivity measurements, it was taken into a flask with beads and immediately defibrinated.

EFFECT OF POSTERIOR LOBE EXTRACT

The profound effect of intramuscular injection of a commercial extract of a pituitary solution of the posterior lobe of the pituitary body on the water intake and the urine output is clearly brought out in Figure 1. As nearly as could be determined, the effect was evident in about one hour following the administration. For the first three days no posterior lobe extract was administered. On the first day it will be noticed there was considerable disparity between the intake and output. This was undoubtedly due to an error in counting the flasks on the part of attendants, who were not accustomed to the routine, as the weight remained constant. On the following day the water intake was restricted for twenty-four hours, but the patient excreted about 5,400 c.c. more urine in this day than she took fluids. Figure 2 shows that on this second day the patient lost 11½ pounds in weight. This loss is accounted for by the excess urine output over the water intake. On the following day, December 5, the patient kept some of the ingested fluid and recovered some of her admission weight. On the three following days, December 6 to 8, the patient was given posterior lobe extract, 1 c.c., three times daily, intramuscularly. Although she was allowed water at discretion, the tremendous drop in water intake and urine output will be noted. Her thirst was greatly diminished and the weight remained practically constant for the three days. December 8, or the third day of the posterior lobe extract period the fluids were again restricted to a much greater degree than on December 4, but on the 4th she passed a great excess of urine over the intake and was very uncomfortable, while on the 8th under posterior lobe extract the output was only slightly in excess of the intake, the

weight fell about 3 pounds and the patient suffered only moderate discomfort from thirst. From December 9 to 11, inclusive, no posterior lobe extract was given and no fluid restriction imposed. The output and intake reached a higher figure than we have ever seen recorded. On each of the following three days, or from the 12th to the 14th, inclusive, the patient was given 1 c.c. of posterior lobe extract, and it will be noticed that the intake and the output were about one-third of what they were when she received 3 c.c. daily. The weight gradually crept up on these three days to near her admission weight. December 15 the fluids were again restricted and the patient given 3 c.c. of posterior lobe extract. From 5 p. m. until the following morning, December 16, at 10 a. m., restriction of water was made as severe as

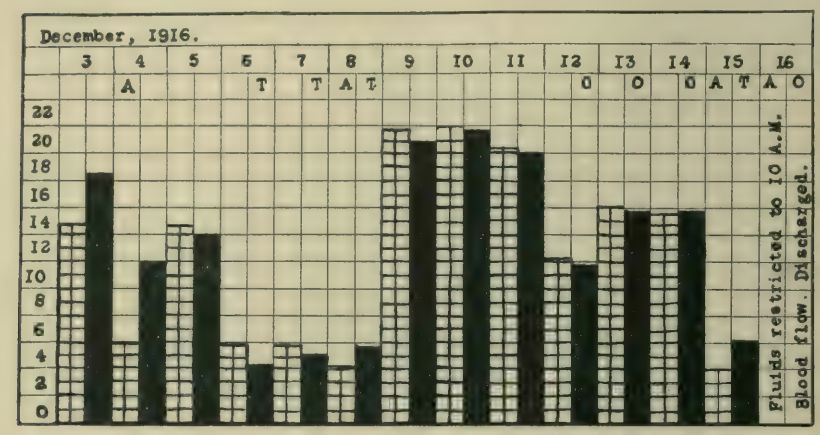


Fig. 1.—Quantity of intake and output per day expressed in liters. Hatched column, intake; solid column, output. On days marked with an A, fluids were restricted; other days there was no fluid restriction. Days indicated by a T, posterior lobe extract was given in 1 c.c. dose, intramuscularly, three times daily. Days marked with an O, a single dose of posterior lobe extract was given intramuscularly.

possible to see whether any effect could be produced on the conductivity of the serum and its relative volume. The patient in the twenty-six hours ending at 10 a. m., December 16, lost 6 pounds in weight.

While the antidiuretic effect of posterior lobe extract given intramuscularly was extremely evident, we were not able to show that the drug prepared for oral administration exerted the same beneficial results, although the results have not been completely negative. Our experience with the oral administration of fresh posterior lobes from cattle has been so far about the same as with the oral administration of the prepared extract. Of course, it is obviously impossible to continue the injections, for it would require at least three a day to keep

the patient in comfort, as the effect lasts only from five to seven hours. After that time there is complete escape from the effect. Larger doses, 2 c.c. per injection, were no more satisfactory; in fact, less so, for the effect did not last any longer and there were more unpleasant accessory actions, as increased irritability of the bladder, with frequent desire to urinate.

As regards the effect of the drug on the blood pressure, the systolic pressure was never found above 130 mm. of mercury, and the diastolic ranged near 75 mm. Although this patient had a hypertrophied heart with dilatation, we felt there was no contraindication to continuing the injections. No change was noted in the blood pressure following the administration.

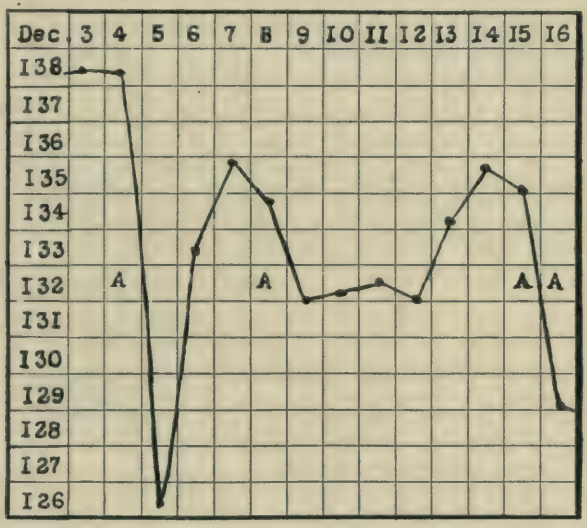


Fig. 2.—Represents the weight of the patient expressed in pounds. These weights were obtained at 8 a. m. On days marked with an A, fluids were restricted.

CONDUCTIVITY AND RELATIVE VOLUME OF SERUM

Table 1 shows the results of observations on three specimens of blood and serum. Although the number of specimens was not as great as could have been wished, owing to the reluctance of the patient, the results seem to show clearly enough a definite although slight increase in the conductivity of the serum and a correspondingly slight decrease in its volume relatively to that of the corpuscles when the intake of water was greatly diminished, either by actual restriction or by giving posterior lobe extract, which lessened the thirst. December 11, as will be seen from Figure 1, the patient took in and excreted over 20 liters

of water. December 15, under posterior lobe extract and slight water restriction (Table 6), the intake was only 4 liters and the excretion by the kidney 6½ liters.

In the seventeen hours preceding the collection of the blood specimen, December 16, water was restricted as much as possible (little more than 1 liter). It will be seen (Table 1) that the conductivity of the serum of December 16 is the highest, and its relative volume the lowest of the three specimens, while the corresponding numbers for December 16. The relative volume of the serum was determined both by the electrical method and the hematocrit. While the hematocrit only gives relative results on account of the difficulty of reaching an absolutely constant end-point, the fact that the longer the centrifugalization is continued the nearer do its readings come to those of the electrical method, confirms the accuracy, at least for comparative purposes, of the results.

TABLE 1.—Showing Conductivity and Relative Volume of Blood Serum

Date	$K \times 10^4$ at 5 C.		Percentage Volume of Serum by	
	Blood	Serum	Electrical Method	Hematocrit*
12/11	54.6	78.6	82.9	79 (6½ min.) 80 (13½ min.)
12/15	52.4	79.5	80.2	76.5 (7 min.) 77.5 (12 min.) 78 (17 min.)
12/16	53.7	82.5	79.0	73 (14 min.) 74.8 (21 min.) 75.7 (21 min.) 76.5 (36 min.)

* Turned at rate of 4,000 revolutions per minute.

The differences in conductivity do not seem to be even as great as those observed by Wilson and by Haldane and Priestley, in whose observations the variations in the quantity of water transported by the blood were much smaller. It must be remembered that the blood is simply the transportation system for the water, and the amount in transit at any moment is no more an index of the amount transported per hour or day than the number of cars of wheat on a railway on a given day are an index to the size of the wheat crop. While it would not be justifiable from so small a number of observations to draw the conclusion that the kidney is stimulated to increase its excretion of water by an even smaller excess of water in the blood in diabetes insipidus than in health, the suggestion may be made that if the kidney is really abnormally sensitive to water excess, so that the threshold of the stimulus is lowered, it would afford an explanation of the condition. It must be remembered, however, that in this patient the pro-

portion of plasma in the blood is greater than normal, so that, on the assumption that the total volume of blood is not less than normal, the addition of a given amount of water to the blood would not dilute the plasma so much or increase its relative volume so much as in a normal person.

MEASUREMENT OF THE BLOOD FLOW IN THE HANDS

This was done on four days by the method previously described by one of us.[14] The idea was to see whether posterior lobe extract caused any definite effect on the blood flow through the superficial vessels at the time when it was causing a decrease in the diuresis. If its antidiuretic effect was associated with an alteration in the flow through the superficial vessels (not associated with a change in the heart's action, which there was no reason to suspect), it was argued that this would render it more probable that vascular reactions were occurring elsewhere, as in the kidney, which might account for the diminution in the excretion of the urine. A dilatation in peripheral areas might very well be associated with a renal constriction. Unfortunately, the existing dermatitis on the patient's hands rendered them peculiarly susceptible to contact with water, so that the uniformity of results in the control observations was less than is usually seen under hospital conditions. She said the water increased the irritation, and she had a similar objection to protecting the skin by oil or vaselin, so that it proved impossible to get as many observations as we desired. The skin affection and the anemia, which is always associated with subnormal hand flow, rendered the exposed parts abnormally susceptible to changes of temperature in the wards. In spite of these drawbacks, however, the four experiments carried out, the condensed results of which are given in Table 2, do seem to indicate an increase in the hand flow under the influence of posterior pituitary lobe extract.

The highest flows were seen on December 15, when the antidiuretic effect was well established. Not only was the flow decidedly better than in the two control experiments (on December 11 and December 14) when no posterior lobe extract was being given, but the flow was steady practically from the time the hands were put into the calorimeter, and did not slowly creep up over a considerable period of time, as in the control experiments. This slow, almost reluctant, increase is a feature of the flow in the hand when its vessels have an abnormally great tendency to vasoconstriction, and when the maximum flow is reached it will then, in any case, be small. Both criteria, therefore, indicate that on December 15 the posterior lobe extract had to a considerable extent overcome the tendency to cutaneous vasoconstriction. The measurement of December 16, although it gave a somewhat lower flow than

14. Stewart, G. N.: Heart, 1911, **3**, 33.

the first control measurement (of December 11), is not really out of harmony with this. The patient had received no posterior lobe extract for seventeen hours, but one hour before the measurement was started she was given 1 c.c. Also she had lost six pounds in weight during the previous period of water restriction, and much of the water she was now taking was not being excreted by the kidneys, but was going back into the tissues. Furthermore, she had been sitting around the ward, as she wanted to leave the hospital, and said that she had been cold all the morning. Her hands were cold when they were put into the bath. The patient said she had noticed that after receiving the injections the skin of the hands, which was habitually dry, became more moist and that her hands, which were habitually cold, became warmer. We confirmed the statement that sweat appeared distinctly on the hands when she was under the influence of posterior lobe extract, while at other times they were extremely dry.

TABLE 2.—Blood Flow in the Hands—

Date	Pulse Rate	Temperature (C.) of Room	Temperature (C.) of Arterial Blood	Temperature (C.) of Calorimeters Right	Temperature (C.) of Calorimeters Left	Volume of Hands in C.c. Right	Volume of Hands in C.c. Left	Heat Given Off in Grams, Calories Right	Heat Given Off in Grams, Calories Left	In Min.
12/11/16	78	24.0	36.92	31.81	31.75	347	360	573	761	10
		24.0		31.88	31.86			725	1,032	10
12/14/16	75	24.4	36.58	31.75	31.72	357	362	237	270	10
		25.4						348	315	10
12/15/16	84	24.0	36.90	32.03	32.07	366	358	933	1,108	10
		24.5		32.17	32.26			930	1,092	10
12/16/16	78	24.2	36.90	31.30	31.35	357	358	602	754	10
		24.8		31.35	31.45			652	855	10

The dermatitis was worse on the left hand and arm, which probably accounts for the greater flow in that hand on December 11, 15, and 16. That the inequality was due to a vasomotor and not to a mechanical difference is shown clearly in the experiment of December 14, when, under the influence of markedly increased vasoconstriction due to cold (two of the fingers on the right hand had been "dead" earlier in the day, she said), the inequality disappeared. If the flow for the second and third ten-minute periods of the experiment be added, they are practically equal for the two hands.

ABILITY OF THE KIDNEY TO CONCENTRATE THE URINE

Erich Meyer[15] advanced the hypothesis that the diuresis of diabetes insipidus is primarily the result of a disease of the kidney. Such a

15. Meyer, Erich: Deutsch. Arch. f. klin. Med., 1905, **83,** 1; Ztschr. f. klin. Med., 1912, **74,** 352.

view has been maintained essentially on the assumption that the kidneys of patients afflicted with diabetes insipidus were not able to elevate the concentration of the urine. Mosenthal[16] has recently offered evidence in favor of Meyer's hypothesis. Histologic examination of the kidneys in diabetes insipidus lends no support to the view that the condition is due to any structural alterations in these organs.

There are now quite a few instances recorded in the literature of patients afflicted with diabetes insipidus whose kidneys have shown definite concentrating ability. Fitz,[17] in this country, has reported a case in which he was able to demonstrate a moderate ability on the part of the kidney to elevate the specific gravity of the urine. Both Motzfeld[12] and Eisner,[13] by the use of pituitary extract injections, were able to show the same thing, only to a more marked degree.

Our patient had a severe anemia, which in itself is sufficient to impair the ability of the kidneys to concentrate the urine, as has been

—OF A PATIENT WITH DIABETES INSIPIDUS

Blood Flow in Gm. per Minute		Flow per 100 C.c. of Hand per Minute		Period in Calorimeter	Remarks
Right	Left	Right	Left		
12.46	16.35	3.59	4.54	First ten minutes	No posterior lobe extract
15.98	22.66	4.60	6.29	Second ten minutes	
5.45	6.17	1.52	1.70	Second ten minutes	No posterior lobe extract
7.94	7.14	2.22	1.97	Third ten minutes	
21.29	25.49	5.81	7.12	First ten minutes	Posterior lobe extract action
21.84	26.15	5.96	7.30	Second ten minutes	
11.94	15.09	3.34	4.21	Second ten minutes	Doubtful posterior lobe extract action
13.05	17.43	3.65	4.86	Third ten minutes	

recently shown by Mosenthal,[16] Christian[18] and unpublished data accumulated by one of us (C). Probably if it had not been for this disturbing element our results would have been more striking than they are.

In studying the concentrating ability of the kidneys the patient was put on a standard Mosenthal renal test diet. This diet contains 13.4 gm. of nitrogen, 8.5 gm. of sodium chlorid and 1,760 c.c. of fluids. No alterations were made in the procedure except to elevate the quantity of water served at each meal. Days when these test diets were run have been indicated in Figure 1 by the term "water restriction." On all of the days when the patient was taking the renal test diet no attempt was made to restrict the patient's water intake after

16. Mosenthal: THE ARCHIVES INT. MED., 1915, **16,** 733.
17. Fitz: THE ARCHIVES INT. MED., 1914, **14,** 706.
18. Christian: THE ARCHIVES INT. MED., 1916, **18,** 429.

8 p. m. So in reality we only made twelve-hour observations; but for completeness the "night" urine was balanced for estimating total nitrogen and chlorid output.

Table 3 shows the response of the patient's kidneys to a renal test meal on November 27, six days before our more accurately controlled period began. No posterior lobe extract was given. The diuresis was not so great on this day as it had been on other days, and the specific gravity of the night urine was distinctly higher than usual. The excretion of nitrogen and salt was perfectly normal. Although there was moderate fixation of the specific gravity, the percentage excretion of salt and nitrogen would indicate definite concentrating ability on the part of the kidney.

TABLE 3.—Response of Patient's Kidneys to a Renal Test Meal Without Posterior Lobe Extract

Time	Amount, C.c.	Sp. Gr	Chlorids	Per Cent.	Nitrogen	Per Cent.
8 to 10	1,226	1.000				
10 to 12	955	1.000				
12 to 2	1,150	1.004				
2 to 4	750	1.003				
4 to 6	400	1.005				
6 to 8	615	1.003				
Total day	5,096	.....	4.59	0.09	5.79	0.11
Night, 8 to 8	1,315	1.007	3.29	0.24	5.67	0.43
Total output	6,411	.....	7.88	....	11.46	
Intake	6,810	.....	8.5	....	13.4	
Balance	+399	.....	+0.62	....	+1.94	

It was thought that if extreme water restriction were imposed with the patient under the régime of a renal test meal and no posterior lobe extract, that the concentrating ability of the kidney might be made more evident than in Table 3. Table 4 shows the result of such an observation on December 4. This was the second day of the observation period and during the first ten hours the patient was restricted to 1,760 c.c. of water. It was necessary to terminate the observation at 6 p. m., and allow water. It will be seen that the patient excreted 5,400 c.c. more fluid than she took in and lost 11½ pounds in weight, as shown in Figure 2, on December 5. The nitrogen and salt were not determined in this instance, but it will be noticed that the concentrating ability of the kidney was only slightly in evidence.

TABLE 4.—URINE CONCENTRATION UNDER EXTREME WATER RESTRICTION WITHOUT POSTERIOR LOBE EXTRACT

Time	Amount, C.c.	Specific Gravity
8 to 10	1,885	1.003
10 to 12	722	1.002
12 to 2	1,270	1.005
2 to 4	1,075	1.007
4 to 6	910	1.007
Total day	6,962	
Night, 6 to 8	5,600	1.002
Total output	11,562	
Intake	6,160	
Balance	—5,402	

TABLE 5.—SHOWING RESPONSE OF PATIENT'S KIDNEYS TO A RENAL TEST MEAL

Time	Amount, C.c.	Sp. Gr.	Chlorids	Per Cent.	Nitrogen	Per Cent.
8 to 10	320	1.001*				
10 to 12	100	1.011				
12 to 2	100	1.013				
2 to 4	155	1.010				
4 to 6	135	1.015				
6 to 8	207	1.006				
Total day	1,017	.....	2.01	0.2	3.27	0.3
Night, 8 to 8	4,370	.....	3.49	0.08	5.87	0.13
Total output	5,387	.....	5.50	....	9.04	
Intake	4,210	.....	4.40	....	12.60	
Balance	—1.177	.....	—1.10	....	+3.54	

* 1 c.c. posterior lobe extract 9 a. m., 3 p. m. and 9 p. m.

Table 5 represents the response of the patient's kidneys to a renal test meal given December 8 of our period of observation. The patient, as shown in the table, received three intramuscular injections of posterior lobe extract of 1 c.c. each, at 9 a. m., 3 p. m. and 9 p. m. In this experiment, as well as in the subsequent one, it will be noticed that

the 9 a. m. dose of posterior lobe extract did not show any marked effect until after 10 a. m. It will be seen, however, that there is a distinct ability on the part of this patient's kidneys to elevate the specific gravity of the urine. The nitrogen and salt elimination appear normal. There seems to be a tendency, however, for the solids to be excreted in greater quantities during the night. But this was just as apparent when the patient was not under the influence of the drug. The effect of the dose given at 9 p. m. usually wore off between 2 and 4 a. m.

Table 6 shows the results of a test diet day on December 15 of our period of observation. The results confirm those shown in Table 5, although the patient did not seem to get so much under the effect of the three doses of posterior lobe extract as she did in that instance.

TABLE 6.—Results on Urine of a Test Diet

Time	Amount, C.c.	Sp. Gr.	Chlorids	Per Cent.	Nitrogen	Per Cent.
8 to 10	1,010	1.001*				
10 to 12	230	1.012				
12 to 2	922	1.004				
2 to 4	360	1.007				
4 to 6	162	1.012				
6 to 8	124	1.007				
Total day	2,808	.....	4.40	0.15	3.75	0.13
Night, 8 to 8	3,710	1.001	4.04	0.11	5.35	0.14
Total output	6,518	.....	8.44	....	9.10	
Intake	4,010	.....	4.25	....	11.88	
Balance	—2,508	.....	—4.19	....	+2.78	

* 1 c.c. posterior lobe extract 9 a. m., 3 p. m. and 9 p. m.

There was a phenolsulphonephthalein excretion of 70 per cent. in two hours. Blood urea was twice estimated. Two hours after an essentially carbohydrate breakfast it was 0.017 gm. per 100 c.c. The urea index at the same time was 157. Another blood urea estimation two hours following a protein meal gave 0.028 gm. per 100 c.c. and a urea index of 81.

We can conclude, then, that with posterior lobe injections this patient's kidneys had ample ability to concentrate the urine. Without the drug there was evidence that the kidneys had only a meager ability to elevate the specific gravity. Other functional tests all indicated a normal kidney excretion.

SUMMARY

The regulation of the excretion of water by the kidney was studied in a case of diabetes insipidus. It was supposed that on account of the high degree of the diuresis, the great quantity of water ingested and transported, and the marked diminution in the excretion and ingestion caused by pituitary posterior lobe extract, the conditions for such a study would be unusually favorable.

The conductivity of the blood serum was slightly increased and the relative volume of serum slightly diminished when the water excretion was lessened by posterior lobe extract or by water restriction.

The blood flow in the hands seemed to be increased during the antidiuretic action of posterior lobe extract. This, so far as it goes, supports the view that a vascular effect in the opposite direction on the renal vessels may be responsible for the diminution in the urine excretion.

It was shown that under the action of posterior lobe extract the kidneys had the power of effecting a considerable concentration of the urine. Other kidney functional tests gave a normal response. Accordingly, no indication was obtained that the condition was in any way associated with a pathologic alteration in the kidney.

MULTIPLE HEMANGIOMAS OF THE SKIN ASSOCIATED WITH DYSPITUITARISM *

GEORGE DOUGLAS HEAD, B.S., M.D.
MINNEAPOLIS

Scattering angiomas (telangiectases) of the skin are frequently found in apparently normal persons and have no pathologic significance. On the other hand, they may develop in large numbers and in varying sizes on the skin of persons with diseases of the liver (cirrhosis and cancer), in chronic jaundice from gallstones, or simple catarrhal jaundice, also in tertiary lues (S. Ehrmann,[1] Trawinski[2]), and as a result of Roentgen-ray skin exposure (Kingsbury[3]).

A family form of multiple telangiectases of the skin and mucous membranes, with recurring epistaxis, has been described by Osler,[4] and later by Hanes[5] and Langmead.[6]

In this group of cases the dilated capillaries are confined largely to the mucous membranes of the mouth and nose and the skin of the face. The tendency to recurring nasal hemorrhages is a prominent feature and there is an hereditary history of recurring hemorrhages in the family.

An exceedingly rare form of generalized telangiectases (telangiectases circumscripta universalis) involving the skin of the trunk, the arms and legs has also been recognized by Brocq[7] and Vidal[8] (quoted by Osler) and by Osler[9] himself.

In this condition the spots are not raised above the surface of the skin. They vary in size from 2 to 6 mm. in diameter and often coalesce in large blotches. No individual blood vessels are seen, and the condition is confined to the capillaries.

A case of multiple telangiectases of the face, mouth, lips, cheeks, sides of neck and upper chest, without hemorrhages and with enlargement of the right lobe of the thyroid gland, has been recorded by Adamson.[10]

* Submitted for publication March 12, 1917.

1. Wien. med. Wchnschr., 1907, No. 16, p. 778.
2. Monatsh. f. prakt. Dermat., 1910, **1,** 45.
3. Jour. Cutan and Genito-Urin. Dis., **29,** 242.
4. Bull. Johns Hopkins Hosp., **12,** 333.
5. Bull. Johns Hopkins Hosp., **20,** 63.
6. Proc. Roy. Soc. Med., **3,** No. 5.
7. La pratique dermatologie, **4.**
8. Bull. et mém. Soc. méd. d. hôp. de Paris, 1880-1881, p. 186.
9. Bull. Johns Hopkins Hosp., **18,** 401.
10. Proc. Roy. Soc. Med., **2,** Part 1, p. 128.

Angiomas of the skin associated with clinical manifestations of pituitary gland changes do not seem to have been observed. Pierre Marie,[11] in Case 2 of his original description of acromegaly, speaks as follows relative to the vascular changes:

> With regard to the circulation and blood vessels, there is one thing to note, the tendency to varicose veins which existed in Case 2. In this patient, in fact, there were not only distinct venous dilatations, with varices, but also large hemorrhoids, which caused much suffering and very abundant loss of blood.

Cushing,[12] while describing peculiar boggy recurring edemas of the skin on the paws, over the face and in the submental regions of a number of his second series of dogs, mentioned no changes in the vessels of the skin, nor is reference to be found of angiomas of the skin in any of the clinical cases reported in his monograph.

Dunn,[13] in reporting a case of acromegaly, mentions "distention of the supra-orbital veins," but states that this distention became evident on exertion or excitement. No reference is made to telangiectases on the skin, mucous membranes or elsewhere on the body.

The two cases here reported are remarkable examples of multiple hemangiomas of the skin associated with clinical manifestations of pituitary gland changes. In Case 1, the skin of the scrotum, penis, inside of the thighs, arms, back and abdomen was affected. In Case 2 the skin of the scrotum and the mucous membranes of the lips and mouth were involved. The case reports are as follows:

REPORT OF CASES

Case 1.—*History.*—Carl L., aged 28, Swedish, single, farmer, was admitted to the University Hospital, Oct. 27, 1913, complaining of pains in the hands, feet and head.

The patient's family history was unimportant, except that his mother had died of apoplexy. Four brothers and three sisters were living. The patient denied venereal disease. He used tobacco and drank moderately of beer and whisky.

At 8 years of age he had influenza, and measles at 12 years. When about 10 years of age he developed a left-sided inguinal hernia which still persisted. There was no history of nosebleed.

The present symptoms of which he complained date back to his childhood. When about 8 years of age he was taken sick with some kind of illness associated with fever, which was called "la grippe." Following this sickness, of which he could give no accurate account, he began to have severe pains in his hands and feet. The pains were not severe enough to call a physician. He remembered that some swelling occurred in the hands and feet along with the pains. After recovery from this illness he was fairly well until about one year later, when he was in bed for six weeks with fever, and pain and swelling in the hands and feet. The pain was confined to the smaller joints.

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12. The Pituitary Body and Its Disorders, Philadelphia, 1912, p. 19.
11. Tr. New Sydenham Soc., London, 1891, p. 12.
13. Am. Jour. Med. Sc., **148,** 127.

It was since this second illness that the patient dated the pains of which he complained at the time of examination. He had suffered intermittently from these pains in the fingers and toes for the previous eighteen years. At first only the hands and feet were involved, but in the previous three years the pains had gone into the long bones of the arms and legs. The pains were deep and boring in character, and came and went without any regularity. He might be almost entirely free from them for days or even weeks, and then they would return and become so severe that he could hardly stand them. Accompanying the pains was slight swelling of hands, feet and face. As a rule he was not bothered as much at night as during the day. The pain was confined to the long bones of the extremities.

On account of these pains the patient had not been able to do much work. From the time the pains began until the age of 16 he suffered a good deal; then for a number of years he was bothered much less. For the three years

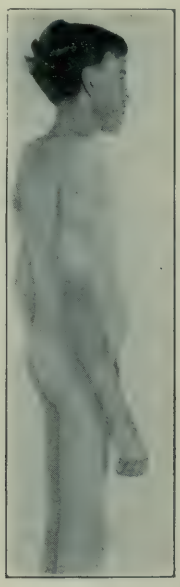


Fig. 1.—Carl L., Case 1, University Hospital No. 5380, patient with dyspituitarism.

prior to examination he had more pain. He thought there was some relationship between the pain and his bowel condition. If he took a cathartic and the bowels moved freely, he had much less pain, but if he became constipated, the pain in the limbs was worse. For this reason he had taken cathartics. At the time of examination he was bothered with attacks of diarrhea, although he was taking no cathartics. Between the ages of 22 and 25 years he increased in stature 3 inches. The telangiectases on the skin appeared when he was about 14 years of age. He noticed them first on the penis and scrotum; later, on the inside of the thighs, while about one year later they began to appear on the outer surfaces of the arms above and below the elbows and also on the back and abdomen. He was sure more of them were coming all the time. None could be seen on the mucous membranes of lips, inside of mouth or nose. The patient said that these spots came on without any burning or itching of the skin. He had never noticed any relationship between the appearance of the spots on his skin and the pains in the limbs.



Fig. 2.—Profile of patient, Case 1.

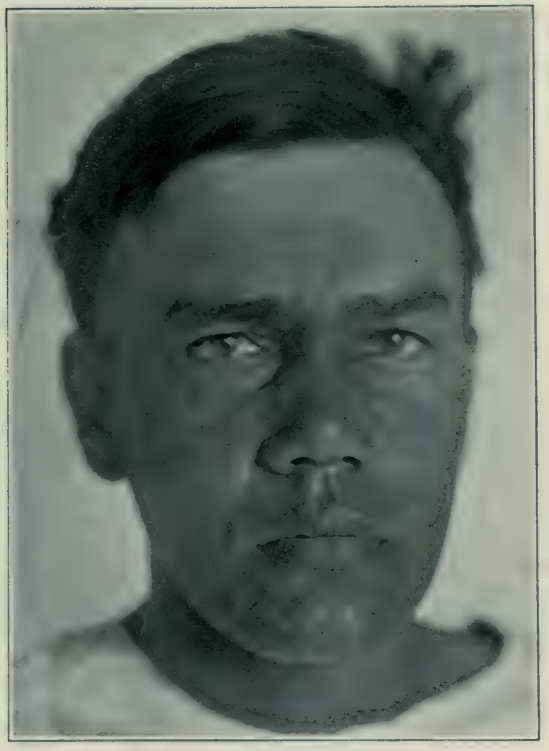


Fig. 3.—Front view of patient, Case 1.



Fig. 4.—Patient, Case 1, showing spacing of teeth.



Fig. 5.—Patient, Case 1, showing telangiectases over skin of back, and hemangiomas of scrotum.

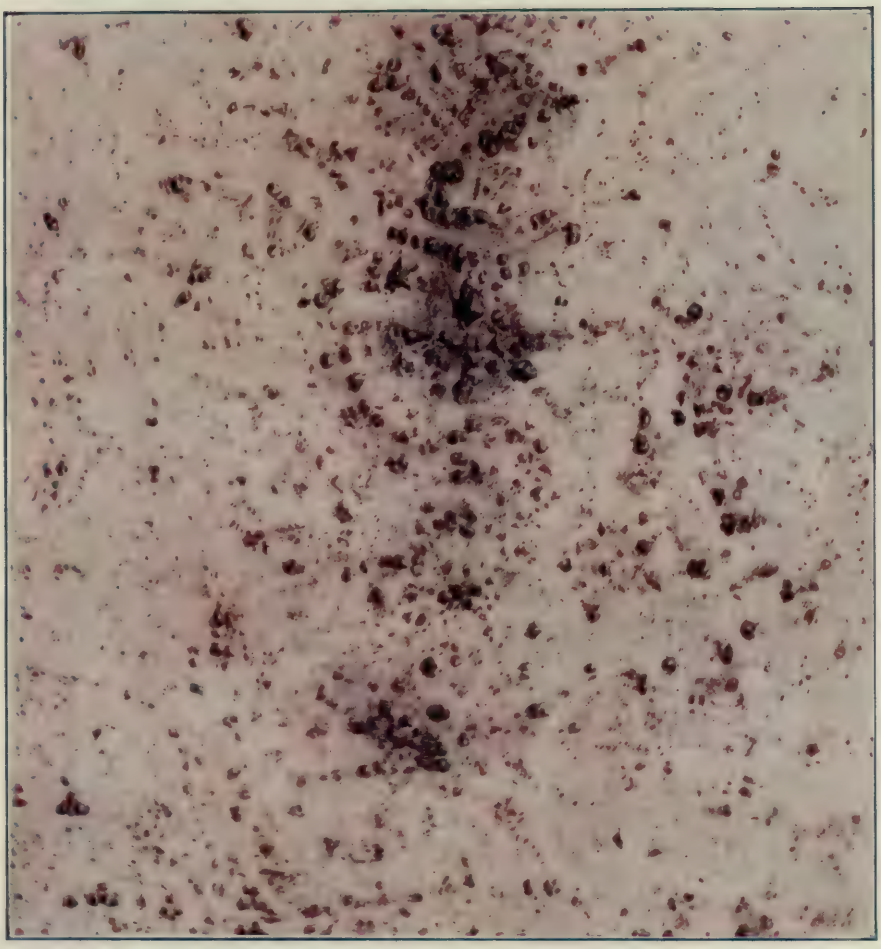


Fig. 6.—Patient, Case 1, skin of the back, showing multiple telangiectases.

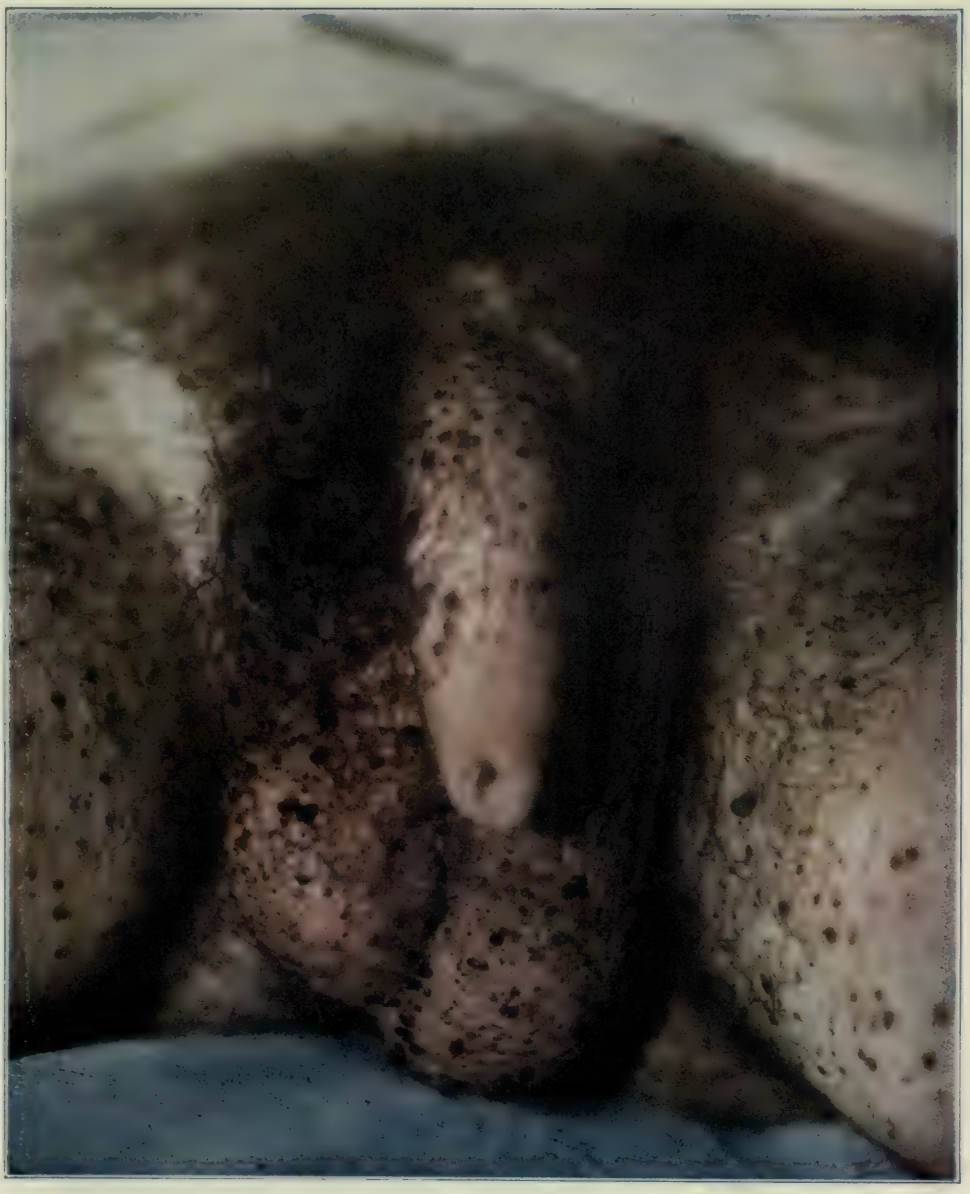


Fig. 7.—From a photograph in color, Case 1, showing hemangiomas of the skin of the scrotum and inner aspect of the thighs.

Physical Examination.—The patient was a man 5 feet 8 inches tall, of rather slender build, with long, slender arms and legs; narrow, lady-like hands and feet; long, slender fingers and toes; funnel-shaped chest; narrow waist; little fingers on either hand curved outward; no lameness or swelling in joints; muscles poorly developed. The patient stood stoop-shouldered (Fig. 1); shape of head in profile was an elongated oval; features coarse and prominent; chin narrow and projecting well forward (Fig. 2); prominent nose, wide at base, dilated alae nasi; slanting forehead; deep-set eyes; prominent frontal ridges; heavy, coarse hair; large ears; thick lips (Fig. 3); teeth spaced (Fig. 4) with some caries and pyorrhea; high palatine arch.

In looking over the skin one was struck with the remarkable development of hemangiomas in various parts of the body. These were present on the face, neck, upper chest, upper abdomen, upper part of back and inner surfaces of arms and legs. The feet and hands were largely free, although here and there on the inner aspects of the arms and legs a few pinpoint, sharply outlined, dark red spots could be seen. They were present in large numbers over the back (Fig. 5) from the angle of the scapulae downward to the buttocks, over the lateral surfaces of the chest, over the hips and lower abdomen from the transverse umbilical line downward on the scrotum and penis, the anterior, lateral and posterior surfaces of the legs and thighs and dorsal surfaces of the forearms below the elbows.

These telangiectases varied in size from a pinpoint to 2 mm. in diameter. The largest were raised above the skin and could be plainly palpated. In some skin areas, such as the lower back (Fig. 6) and over the scrotum and penis, they were present in enormous numbers and so thickly set as to cover almost every part of the skin. In color, the largest were very dark red and the smallest bright red. Over the scrotum and penis, and in some areas adjoining on either thigh, these dilated venules stood out in fringe-like projections 4 and 5 mm in length. These were thin and delicate, and when pressed firmly the blood could be squeezed out, leaving a white blanched appearance. Some of the largest tufts had pedicle-like bases 5 mm in diameter, with rounded apices (Fig. 7).

A careful physical examination of the patient was negative for organic disease. The pupils reacted to light and accommodation; knee jerks active; no ankle clonus; plantar reflex normal; no Kernig sign; no swelling in joints; no muscular atrophy, but a general lack of muscular development; tactile sensation intact; skin normal to heat and cold; no local tenderness along nerve trunks; blood normal; urine negative, except for a trace of albumin; the ingestion of 200 gm. of glucose caused no glycosuria; Wassermann test negative; subcutaneous tuberculin test (7 mg.) negative; spinal fluid Nonne test faintly positive; cell count less than one cell per c.mm.; very few lymphocytes.

The sella turcica measured 12 mm. (Bissell). Portions of tufts of dilated capillaries on the scrotum were removed and sent to the hospital pathologist.

Pathologic diagnosis, hemangiomas of skin (W. C. Johnson).

Clinical diagnosis, dyspituitarism; hemangiomas of skin; scrotal hernia.

Note made Sept. 29, 1914:

"Patient comes again into the hospital for further study. Says he is feeling only fairly well. Some days he feels better and other days worse. Complains mostly of pains in toes and fingers, with dull aches in knees. Sometimes he will go for two or three days without any pain, and then again the pains will come on and continue for from one to two weeks. The pain is sharp, sticking, steady, coming in waves, with intervals of more or less relief. Has ill-defined pains in upper abdomen, especially after he eats such things as apples, potatoes, etc.

"As the patient lies in bed he is apparently comfortable. In complaining of any distress the forehead is wrinkled. Lower jaw is prominent; over-hanging hairy eyebrows; nose large and broad at base; slanting forehead; thick lips; large mouth; deep set eyes; large ears; mucous membrane of lips and cheeks

high color. The hair begins far back on the forehead; is thick and coarse; heavy eye lashes. Clinicians who examined the patient on previous admission agree that his features are larger and more prominent than before.

"In profile, the head has elongated, oval shape—narrow, prominent chin at one end of oval and crown of head at the other; large, wide nostrils. Tongue looks narrow when protruded; shows indentation of teeth. Upper jaw fairly broad at base, but narrowed in front by irregular placing of teeth; high palatine arch; front teeth widely spaced and irregularly placed in jaw; molars placed irregularly in jaw and of short, stubby type. Lower jaw narrow; teeth irregularly placed; some projected forward toward lips; others arranged regularly.

"In standing position patient is tall, stoop-shouldered; arms and legs look thin and long (Fig. 1); hands and feet of narrow type, fingers and toes long and tapering. Little fingers on both hands are deformed; tips of each curve inward toward adjoining finger, giving a bowed appearance. Joints of little fingers show no ankylosis, no exostosis.

"Thorax conformation broad at upper part, tapering somewhat at lower thorax, measures 88 cm. in circumference above, and 78 cm. in circumference of lower thorax.

"Abdominal conformation normal; no muscular rigidity.

"Nails long and tapering; convex and smooth.

"Hair over whole of body very light, thin and short. In axillae, groins and over scrotum, hair is black and coarse; well developed.

"Patient states that he does not sweat easily—only a very little in hot weather under arms; skin smooth and thin; free from pigmentation."

A careful physical examination of the patient was again negative for organic disease. The remarkable development of capillary vessels in the skin previously noted was present, vessels in increased numbers being found in the locations formerly described. Neither in color nor in size was any important change to be made out.

The patient remained on the medical service fourteen days. During this period he complained much, at times, of pain in the arms and legs. He did not lose weight. He was finally transferred to the surgical service where the hernia was repaired and the patient discharged.

Case 2.—*History.*—Ole M., man, aged 60, single, American, laborer, was admitted to the University Hospital May 26, 1914, complaining of dyspnea, cough and swelling of the legs.

The patient's family history was unimportant, except that his father and one brother had died of tuberculosis of the lungs. As a child he had had whooping cough and mumps; also had articular rheumatism at 20 years of age. He denied lues. There was no history of nosebleed.

The history and clinical notes of the patient's present illness, dealing with the cardiorenal features of the case, and apparently having no bearing on the condition about to be described, will be omitted from this report.

The clinical diagnosis of endocarditis of the mitral valve, cardiac hypertrophy and dilatation, passive congestion of the liver and lungs, covers this part of the clinical study of the case.

The chief interest centers in the acromegalic features associated with hemangiomas on the skin of the scrotum and mucous membranes of the cheeks and lips. Just when these first appeared the patient could not state with certainty. He first noticed them about six years prior to admission. He did not remember exactly when his hands and feet began to increase in size. He was certain that they were larger than a few years previously and that his features, especially the nose, had increased during the previous two years.

The man was of a dull, stolid appearance and short gorilla type of build. His speech was slow and hesitating. All his movements were sluggish. The head was large and deep-set between the shoulders; forehead sloping and broad; broad, heavy-boned chest; short, thick abdomen; large joints; broad,

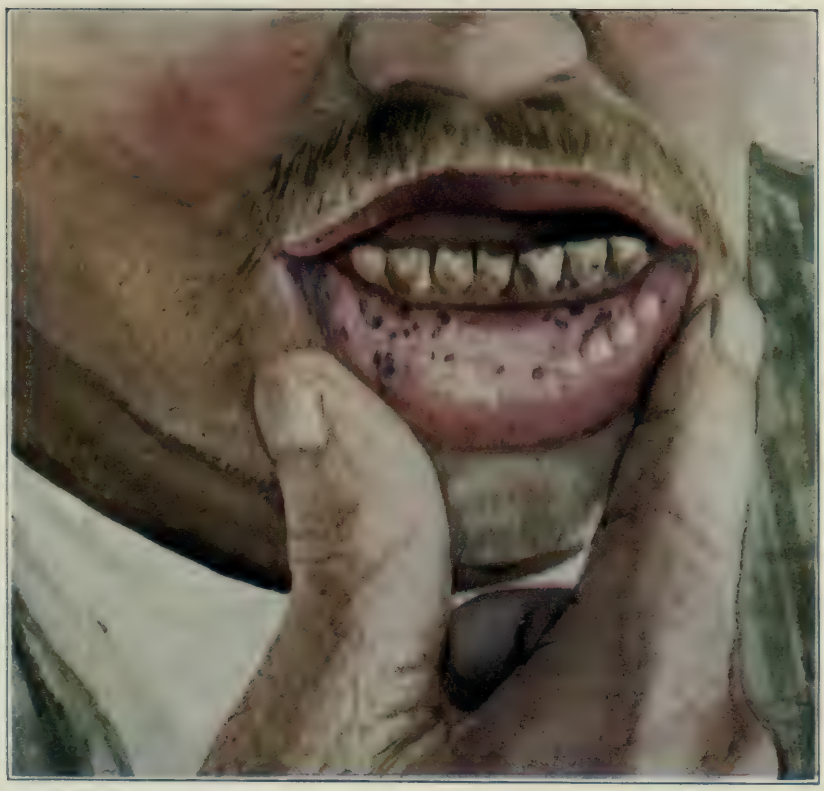


Fig. 8.—Ole M., Case 2, from the University Hospital, patient with acromegaly, showing hemangiomas of the mucous membrane of the lips. Note also the spacing of the teeth and the corrugated appearance of the under lip on the left side.



Fig. 9.—Case 2, showing hemangiomas of the skin of the scrotum.

spade-like hands, with thick, stubby fingers and heavy, brittle nails; broad, flat feet with short toes. He stood stoop-shouldered, with head thrown forward; eyes deep-set; eyebrows shaggy; prominent, large frontal ridges; nose broad, with wide dilated alae nasi; lower jaw heavy, projecting well forward; mouth large and broad; lips thick; cheeks a suffused red color, with many small dilated vessels. When the patient opened his mouth the jaws looked heavy, broad, and shallow, with rami wide apart. The teeth were distinctly spaced, of short, stubby type, irregularly set in the jaws (Fig. 8).

The appearance of the under lip was peculiar. When this was turned down, many large and small tufts of dilated vessels (Fig. 8) could be seen scattered over the mucous membrane. These were more numerous on the right side of the lip and extended well back on the cheeks beyond the angles of the mouth. Some of the dilated venules were pinpoint in size. Others were larger, even 0.5 cm. in diameter, and were markedly raised above the surface of the mucous membrane. In color they were pale purple and dark blue. There were about ten of these on either cheek; twelve or more on the lower lip, and about fifteen on the inner surface of the upper lip. They were round, oval or irregular in shape; in some places confluent. On firm pressure the blood could be partly squeezed out of these vessels and they would partly lose their blue color and become pale, only to assume the dark blue or purple color as soon as the pressure was removed. Over the left side of the lip the surface was cut up with a number of serrations with elevations between (Fig. 8). The mucous membrane of the rest of the mouth, pharynx and throat was free from these hemangiomas. The tongue was large and thick, filling the mouth from corner to corner when protruded.

The hair of the head was thin and coarse, as was also that of the moustache and beard.

A few scattered telangiectases of small size could be seen on the skin of the back. The rest of the trunk and the arms and legs were free.

The appearance of the skin over the scrotum was peculiar and remarkable. Dotting its entire surface were groups of dilated vessels. Some of these were very small—only pinhead in size—and presented the appearance of simple telangiectases, while others were fully 0.5 cm. in diameter and formed distinct tufts of vessels projecting above the surface of the surrounding skin (Fig. 9). The smallest of these were dark red, the larger a dark blue or purple. The hair about the genitalia was thin and coarse.

The patient remained in the hospital eighty-eight days. No change was observed in the features or size of hands and feet during that time. No accurate measurements were made, however. No Roentgen-ray examination of the skull was made.

Blood: red cells, 4,200,000; leukocytes, 7,800; hemoglobin, 86 per cent.

Differential count: small mononuclears, 29 per cent.; large mononuclears, 1.5 per cent.; transitionals, 4.5 per cent.; polynuclears, 64.5 per cent.; eosinophils, 0.5 per cent.

The Wassermann reaction was negative. The urine contained a small amount of albumin, and hyaline casts. Blood pressure: systolic, 156; diastolic, 80.

The cardiorenal features of the case improved steadily up to the time of the patient's discharge, but the hemangiomas remained as distinct as on admission.

No new telangiectases appeared during the patient's stay in the hospital; neither did those present change in their appearance or size.

PHTHISIS PULMONALIS AND OTHER FORMS OF INTRATHORACIC TUBERCULOSIS *

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CHICAGO

In studying a large material such as is available at the Municipal Tuberculosis Sanitarium, one is struck by the fact that intrathoracic tuberculosis does not always manifest itself in the same manner. There come to mind a number of questions regarding the pathology and genesis of these different types of tuberculosis. It is the aim of this paper to present answers to some of these questions. This work is based on Roentgen-ray examinations of over 600 patients, with all forms of tuberculosis, and clinical and laboratory observation of over 2,500 such cases.

BRONCHIAL GLAND TUBERCULOSIS IN CHILDREN

Chronologically, the earliest tuberculosis encountered is the bronchial gland tuberculosis of children. There are constantly in our institution over 100 children under the age of 14 who present practically every type of pulmonary tuberculosis occurring in these ages. The classical work of Ghon[1] on the primary tuberculosis of children has been of great help to us in understanding the disease as we have encountered it. Our clinical and Roentgen observations correspond fully with the findings of Ghon.

Ghon's view that the primary tuberculosis of children is caused by the inhalation of either droplets of tuberculous sputum, or of dried tubercle bacilli, seems to me to be the most logical explanation of the genesis of the primary tuberculosis. Very soon following this primary inoculation there is an involvement of the regional lymph glands. This behavior of the nontuberculous child towards infection with tubercle bacilli corresponds with the experimental data on inoculation tuberculosis in the laboratory. Unless the number of bacilli inoculated is exceptionally great, one usually finds comparatively little evidence of disease at the point of inoculation, but almost invariably finds a more or less marked involvement of the regional lymph glands. I can see no reason for assuming that the human being should react differently than any other animal to such an inoculation. According to the investi-

* Submitted for publication Feb. 23, 1917.

1. Ghon, A.: Der primäre Lungenherd bei der Tuberculose der Kinder, Wien., 1912.

gations of Fluegge[2] the number of bacilli lodging in the lungs in the inhalation experiment is only about 4 per cent. of the total number which enter the respiratory tract. This accounts for the fact that the children do not get an enormous tuberculosis at the point of inoculation, but rather get a mild lesion which has a tendency to heal. The symptoms in these children are caused, not by the primary pulmonary focus, but from the absorption of the toxins which may be formed in the glandular focus. For a more detailed account of the gross pathology of these lesions I refer to Ghon's monograph.

Clinically, these children present histories which are fairly typical. In these histories one may or may not be able to trace the source of infection. If the parents are of average intelligence, however, one can trace the source of infection in a very much larger percentage of cases than is possible in older individuals. Quite naturally, of course, one would hunt this source of infection in the immediate family of the patient. Failing there, one is often able to find it in the close vicinity of the patient's home. Should no source of infection be traceable, however, we must not forget that in a city of the size of Chicago, the opportunity for accidental contacts, especially among the classes from which our patients are drawn, always exists.

Coming to the history of the case itself, we find that, on close questioning, the parents will often say that the child has stopped growing, or does not seem to gain in weight. Along with this the parents will notice that the child does not have the energy that other healthy children have, and does not have the same inclination to play. The child tires easily, is apt to be irritable and cross. The appetite is slightly below par and is often capricious. There may or may not be some digestive disturbance. Often, however, constipation is noted, possibly due to the lack of exercise on the part of the child. Sometimes these children will have nightsweats, and the mother on close questioning will recall that the child has been feverish in the afternoons. There may or may not be a slight cough, which is hacking and unproductive. If the child is going to school the teacher will often complain that he is inattentive and does not seem to be able to keep his mind on the school work. Occasionally one will be able to obtain a history of pleuritic pain. As will be noticed, most of these symptoms are constitutional symptoms which may be present in other conditions such as chronically diseased tonsils, middle ear disease, and other cryptic infections. Undoubtedly many of these little patients have had their tonsils removed in the belief that this was the cause of the constitutional condition.

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2. Fluegge: Die Verbreitungsneise und Bekampfung der Tuberculose, 1908, p. 478.

On physical examination one finds a child that is slightly undernourished, apt to look pasty, slightly anemic, and not seldom stunted in growth. If there are diseased tonsils or middle ears present, there may be a slight enlargement of the cervical glands, which, however, are not necessarily tuberculous. If there are decayed teeth, one is apt to find a similar enlargement of the submaxillary glands. Inspection very often reveals a slight or sometimes marked engorgement of the superficial veins of the chest both anteriorly and posteriorly. The mobility of the chest wall on respiration is seldom retarded, and is usually equal on both sides. There are very rarely evidences of any retraction. A careful percussion of the interscapular region will occasionally

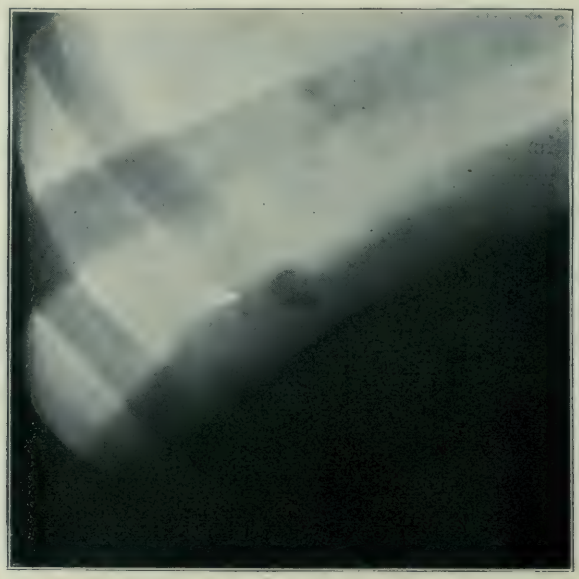


Fig. 1.—Primary tubercle, healed. The shape suggests calcification of a lesion filling out a small alveolar group. (Not reduced.)

reveal a slight change in the note. Often after the fifth or sixth year one notices a slight diminution of resonance over the right apex, anteriorly and posteriorly, which does not necessarily indicate any underlying pulmonary disease. There are usually no evidences of pleuritic adhesions. Auscultation will give a positive D'Espine sign, very rarely any râles, occasionally friction sounds at one base or the other. Along with the slight change of percussion to be found after the fifth or sixth year, one begins to notice a slight increase in the intensity of the breath sounds over the right apex as compared with the left. This discrepancy between the two apices is found from this age on, and may be considered normal.

On observing such a patient for another week or two one will find that the von Pirquet reaction is positive in a very large percentage of the cases. The pulse is unstable, even when the child is kept quiet, ranging in the evenings from 110 to as high as 140. The temperature will also be unstable, sometimes showing marked amplitudes, at other times showing evening rises to 37.5, 37.6 and 37.7 C., and even higher. On prolonged observation over a period of months one notices further a flat weight curve. Even on a carefully selected diet the weight of such children often remains stationary as long as a year before there is any increase.

Laboratory examinations will show no tubercle bacilli in the sputum, which is usually salivary and contains only the ordinary mouth bacteria and a few epithelial cells and leukocytes, such as are commonly found in this type of sputum. As already mentioned, however, most often these patients produce no sputum whatever, so that in this respect the laboratory can give us only negative information. The urinalysis shows negative diazo and urochromogen reactions. Occasionally, if the children are constipated, there is an increase in the amount of indican present; otherwise the urine findings are negative. The blood will show a negative Wassermann, provided, of course, the family history with respect to lues is negative, and in about 50 per cent. will show a positive fixation test with Corper's[3] autolysate antigen. The few blood counts which we have made show, as a rule, from 8,000 to 10,000 leukocytes, which may be considered a very slight increase over the normal; the differential count shows nothing typical of the condition.

The Roentgen-ray examination shows enlargement of the bronchial glands. Sometimes these glands are fairly well circumscribed, without any zone of collateral inflammation about them, indicating that some degree of scarification has taken place; in others the shadows are described by roentgenologists as soft, being quite poorly defined. Occasionally one will notice shadows indicating areas of calcification in these cases. Sometimes one will find all three of the above described types of shadows lying quite close together in the same plate. We assume that these calcified areas are completely healed foci. The primary focus or foci in the lungs themselves are usually not demonstrable on a flat plate. As Ghon says, these primary foci are often of very small size and may disappear entirely, leaving only a slight fibrosis, a condition which would be exceedingly difficult to identify on either flat or stereoscopic Roentgenograms. In making roentgenographic examinations of over 100 such children we have not made stereoscopic plates, partly on account of the expense involved and partly on account of the fact that many of these children are either too timid or not intelligent enough

3. Corper, H. J.: Jour. Infect. Dis., 1916, **19,** 315.

to hold still for the length of time required to make a set of stereoscopic plates. Possibly a large number of patients examined stereoscopically would reveal a larger percentage of primary foci. Whether the primary focus is demonstrable or not, the regional gland involvement is practically always present, and, as we find in experiments on the guinea-pig in the laboratory, the regional gland involvement is usually more extensive than the primary focus at the point of inoculation. As Ghon has shown, these primary foci are fairly well distributed throughout the lungs and are by no means confined to the extreme apices or upper lobes. They are almost as frequently found in the lower lobes as in the upper. The group of glands enlarged usually indicates to the roentgenologist in what sector of the lung he must search for the primary focus. Occasionally one will find indications of a slight thickening of the pleura at one base or the other, and now and then evidences of bronchiectasis in one or the other lower lobes, which is probably caused by constriction of the lumen of one of the larger bronchi, either by pressure from an overlying bronchial gland or as a result of fibrosis stimulated by a diseased gland.

I believe that the above clinical picture of the primary tuberculosis of children can be found quite regularly if one searches for it. From the standpoint of symptoms one will have to rule out the other crypts of infection which may exist. For practical purposes one may say, and be right in 95 per cent. of the cases, that a child giving a positive von Pirquet reaction will show evidences of healed or unhealed bronchial gland involvement. It is unnecessary, then, except for the purpose of absolute accuracy, to make a roentgenogram of all such cases. A careful analysis of such cases as these will be illustrated in another publication.

BRONCHIAL GLAND TUBERCULOSIS OF ADULTS

The bronchial gland tuberculosis of adults may be a recurrence or flaring up of a stationary process, the inception of which dates back several years to a primary tuberculosis of childhood.

The word stationary is used only in a relative sense. Personally, I am not yet ready to believe that any process caused by a micro-organism may remain absolutely stationary. I am rather inclined to believe that after the glandular focus has been formed there is often a state of more or less biochemical balance between the host and the organism which retards the progress of the disease to such an extent that there are no symptoms, and, although extension may take place, it occurs so slowly that we are unable to recognize it. This biochemical balance may at any time be disturbed by a number of factors such as overwork, dissipation, disease, etc. These factors affect the host and not the micro-organism and make it possible for the micro-organism to

grow with renewed vigor. This may possibly explain why some authors believe that the micro-organism may undergo a change in virulence in the animal body or the human body, the cause for which seems to be unknown.

On the other hand, it may be a primary tuberculosis of an adult who has never before come in contact with the tubercle bacillus, so that anatomically and genetically the process is identical with the similar process so often found earlier in life. One must also consider the possibility that there has been a process earlier in life which has



Fig. 2.—Bronchial gland tuberculosis of an adult, with some slight lymphangitic extension toward the right apex.

resulted in complete healing, with lapse of sufficient time for any immunity or hypersensitiveness that may have been established to disappear, to be followed later by a reinfection which would behave similarly to the initial infection in early childhood. I am confident that the first two processes may and do take place. The third must be considered a possibility to be proved or disproved by further observation and research.

These patients may or may not give a history of exposure to tuberculous infection. There have not been so large a number of adult patients with bronchial gland tuberculosis at our disposal as there have been of a similar condition in children, so that it is impossible to work out on a percentage basis the proportion of positive histories concerning the source of infection. Sometimes by careful questioning one can elicit the history of a previous attack of bronchial gland tuberculosis in childhood, but, as a rule, the average adult will not remember a condition which is characterized by such an insidious symptomatology, and one must search for other evidence of previous bronchial gland tuberculosis. The history of these patients is that of a progressive loss of weight extending over a period of several months or longer. There is a slight diminution in the appetite, which is often capricious. There may be slight gastric indigestion, which may be, so far as one can tell by the history, accompanied by either a diminished hydrochloric acid content, or hyperacidity. Sometimes the digestive disturbances will be marked enough to lead the patient to consult a stomach specialist, who will only be able to demonstrate a functional disorder of the stomach, provided of course actual organic disease of the stomach be not coexistent. These patients are very commonly constipated and often have symptoms of intestinal stasis. Along with such a history there is also a history of lack of energy, or, as patients sometimes call it, a slight laziness, and inability to perform the same amount of work as when in good health. There may be a slight afternoon elevation of temperature, with an occasional nightsweat. When these patients are under observation one finds the same instability of temperature and pulse as noted in the bronchial gland tuberculosis of children. They often pass through the hands of a number of physicians without a definite diagnosis being made. There is sometimes a slight, dry cough present, and, if any sputum is raised, it is apt to be mucoid in character and comparatively small in amount. The resistance of such a patient to any acute infection of the upper respiratory tract, as well as practically any other disease, is lowered, and one will often get a history of frequent colds and light attacks of bronchitis. The cough in this case, and probably also the little sputum that is produced, is caused by the irritation of the bronchi by the chronically diseased glands which lie along them. Sometimes these same patients will complain of aching or soreness between the scapulae and along the margin of the sternum.

As will be noted, most of these symptoms are again those that might be caused by any cryptic infection. In making the diagnosis, such cryptic infections must of course be ruled out by careful and systematic search. On physical examination these patients are found to be slightly undernourished, occasionally also slightly anemic and pasty looking. On inspection one may find slight engorgement of the superficial capil-

laries over the upper part of the chest both anteriorly and posteriorly. If there has been a great loss of weight the supraclavicular and infraclavicular fossae are apt to be marked. There is usually no impairment of the chest expansion, or of the mobility of one side of the chest as compared with the other. On percussion one notices usually a slightly diminished note over the right apex anteriorly and posteriorly, and may on very careful percussion be able to outline an area of slightly diminished resonance in the region of the third to the sixth dorsal vertebra along either side of the spine. The mobility of the diaphragm on both sides is about equal. The diaphragm level on the right side may be a trifle higher than on the left, which, however, is not significant. After the fifth or sixth year of life one is apt to notice a slight discrepancy in the level of the two sides of the diaphragm, the right usually being slightly higher than the left. I cannot say that any special significance can be attached to this condition, which I believe is just as often found in the well as in the sick. On auscultation, one may find again a positive D'Espine sign. The breath sounds over the right apex may be slightly accentuated and there may be a slight increase in the intensity of the whispered voice. This, I believe, does not necessarily signify that there is apical disease. One does not usually find râles or evidence of pleuritic disease.

The laboratory examination usually shows negative sputum. If there is sputum, one finds mouth bacteria, a few leukocytes and epithelial cells. There may, however, be tubercle bacilli in the sputum even when there is no demonstrable pulmonary lesion. I have found one such case in which the Roentgen ray and physical examination, as well as careful examination of the larynx and the rest of the upper respiratory tract, revealed no evidence of tuberculous foci except bronchial gland disease. After a few days this patient's sputum became negative and remained so. This condition was caused by the rupture of a tuberculous gland into the bronchus, with discharge of its contents. Such cases are not common, but will be encountered occasionally. The urine examination does not show anything of note except possibly a slight increase in the amount of indican present. The blood may or may not show positive tuberculosis complement fixation. The Wassermann test should be negative unless there is a coexisting syphilis. The leukocyte count may be normal or show a very slight increase, as was found in the case of the children. There may occasionally be blood in the sputum of these patients, due possibly to varicose veins on the surface of a bronchus which are caused by the fibrosis about a diseased gland. It may be remarked here that every hemorrhage from the respiratory tract, without tubercle bacilli or elastic fibers being found after diligent search in the material coughed up, should be suspected as having come from

such a varicosity. Possibly bronchoscopy in such cases would reveal the source of the hemorrhage, and possibly also local treatment might stop the hemorrhage entirely.

The Roentgen-ray findings in these cases show greatly increased hilus markings, the diseased glands casting soft, hazy shadows which may vary in size from that of a nickel to that of a half dollar. The soft hazy outline of these glands is considered to be caused by a zone of collateral inflammation or congestion produced by the disease. Often one is able to locate calcified rests of previous processes in the vicinity. A primary focus may or may not be demonstrable. Quite often there are increased peribronchial markings towards the apices. These strands are often found lying alongside the vertebral column and extend from the diseased gland upward. I believe that these strands, which are often irregular in density and slightly nodular, are caused by a slight ascending lymphangitis tuberculosa, the intensity of which varies in different cases. I doubt very much whether this slight lymphangitis could be responsible for any physical signs.

PHTHISIS PULMONALIS

In children as well as in adults I have been unable to find a step between intra-alveolar larger or smaller bronchopneumonic tuberculosis and bronchial gland tuberculosis. I have been limiting the term phthisis pulmonalis, or pulmonary consumption, to a condition which is actually characterized by destruction of lung tissue, in distinction from other forms of tuberculosis which are not characterized by such destruction. The disease is essentially pneumonic in type, and I believe the genesis of the process is the same whether it is benign, resulting in healing, or whether it is the intensely destructive process which we call ulcerative phthisis.

Phthisis pulmonalis is caused by the reinfection of an already tuberculous individual. If the primary inoculation were sufficient to cause phthisis pulmonalis, why do not more children suffer from this form of tuberculosis? Phthisis pulmonalis may occur in young children, sometimes leading very rapidly to death, and again, in other cases, run a long course, with the same chronicity one so often notices in adults. From a study of the tuberculosis of children, as well as the deductions from Fluegge's work on the number of bacilli which may be inhaled into the alveoli or terminal bronchioli, I do not believe that a person can inhale sufficient bacilli to give rise to this type of tuberculosis, as a primary disease, sufficiently often to cause the large number of cases of phthisis with which every community has to deal. This view is further strengthened by the fact that approximately 70 per cent. of our patients who suffer from phthisis pulmonalis give no history of previous contact

with tuberculosis within a year or two previous to their breaking down with the disease, and in many cases are absolutely unable to recollect ever having been in close contact with a consumptive. I do not believe that an accidental contact such as may occur in street cars, theaters, etc., is sufficient to result in primary inoculation of sufficient intensity to cause phthisis. If such accidental contact were sufficient, the death rate from tuberculosis among physicians, nurses and others working in tuberculosis sanatoriums would be enormous. It is well known that the death rate among such persons is not any higher, and is often lower, than among the general population. Furthermore, such a primary inoculation would of necessity show a bronchial gland disease similar to that found in any primary inoculation, and this is not the case in phthisis. We have paid particular attention to the condition of the bronchial glands in the recent necropsies performed in our institution, and have noticed that even where a massive pneumonic tuberculosis exists, one does not find any greater gland involvement than the roentgenogram indicates in a primary tuberculosis of children. It is not uncommon to find swollen, anthracotic glands, which macroscopically present no indications of tuberculous disease, lying in the midst of consolidated areas. It is well known that the reinfection of a tuberculous animal usually does not result in a regional gland involvement. In human beings Klemperer's[4] experience shows that the same rule holds good. He injected living bovine tubercle bacilli subcutaneously into the forearms of individuals suffering with known pulmonary tuberculosis, as well as others who were clinically well and had never been sick with the disease. The result was a cold abscess at the point of inoculation, which formed very gradually, ruptured, and then slowly healed. There was no regional gland involvement. One is forced, then, to the conclusion that phthisis pulmonalis is usually a reinfection from within of an already tuberculous individual.

Contact with the tubercle bacillus is followed by a state of altered reaction or allergy toward the tubercle bacillus in the human or animal body. This allergy is closely akin to immunity and is by many writers considered an evidence of immunity. We find that such animals withstand reinfection with a dose of tubercle bacilli more than sufficient to kill a nonsensitized animal. Roemer's[5] work on the immunity of sheep illustrates this very clearly. In order to cause a successful local tuberculosis, that is, a tuberculosis which will cause symptomatology and disease in the animal body, a very large dose of tubercle bacilli is necessary. To cause such a disease in the lungs of a sensitized being, a dosage of tubercle bacilli is necessary which could only under the most

4. Klemperer: Ztschr. f. klin. Med., 1905, **56,** 256.
5. Roemer, P.: Beitr. z. Klin. der Tuberk., 1910, **17,** Part 3.

extraordinary conditions be obtained by a reinfection from without. That such a reinfection may take place is proved by the case of Tappeiner's diener, cited by Cornet.[6] In our roentgenographic studies we have run across one such case, in which we found a probable reinfection from without which followed prolonged and very intimate contact with a careless consumptive. If consumption were regularly caused by infection from such prolonged and intimate contact, even our most ignorant patients would remember such contact and mention it in their histories, which, as already said, is by no means the case.

Such a reinfection from without would of necessity be bilateral, because both lungs move simultaneously in the act of breathing, and

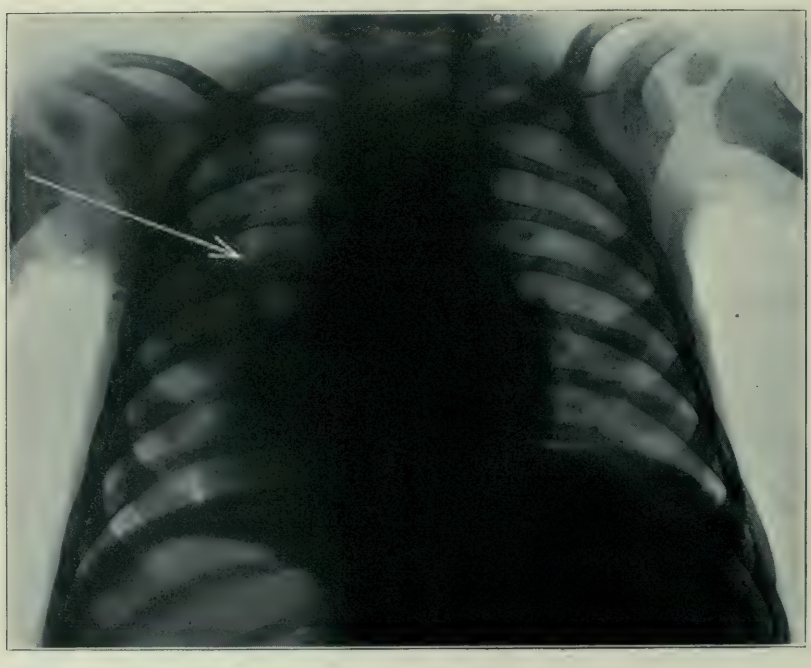


Fig. 3.—Phthisis pulmonalis in a six months' infant. The arrow points to a cavity. Verified by necropsy.

the mechanical forces which govern the aspiration of material are the same in both lungs. As a matter of fact, comparatively few cases of phthisis pulmonalis present the same amount of involvement in both sides of the chest. If the infected material came from above the bifurcation of the trachea, the amount of involvement ought to be practically equal in the two sides, whether it is a case of reinfection from within or without. This discrepancy in the amount of involvement, and the

6. Cornet, G.: Die Tuberculose, Ed. 2, Wien., 1907.

fact that this disease is quite often unilateral in the beginning, indicate that the source from which these bacilli come is fairly close to the point at which the tuberculous disease manifests itself.

This tuberculous material could hardly come from a tuberculosis of childhood that could have lighted up again, on account of the fact that the primary foci of children are found almost as often in the lower lobes as in the upper ones. The ratio between the upper and the lower lobes, disregarding the middle lobe, is 7 to 5 in favor of the upper lobes, with the right upper lobe showing the most primary foci. If the phthisis of the adult were due to a flaring up of such a process, which, as Ghon found, is often small in extent and has a decided tendency toward healing, we should find the beginning of phthisis pulmonalis in the lower lobes more often than we do. I see no reason why the same ratio between the upper and lower lobes should not hold good. We do find occasionally that phthisis pulmonalis begins in one or the other of the lower lobes, but these cases are so rare that one is inclined to believe that the lower lobe process is nontuberculous until proved otherwise. On the other hand, upper lobe tuberculous processes are so common that we consider them tuberculous until proved to be nontuberculous.

There is only one point left from which a massive dose of living organisms could be obtained, and that is from the bronchial glands. These glands when tuberculous may soften and rupture into the bronchus just as easily as tuberculous glands may soften and break through the skin to the outside. In fact, it is possible that the resistance of the bronchial wall to such a breaking through may be less than that of the skin. It is highly significant that Ghon found in approximately 17 per cent. of the children he examined at the necropsy table evidence that such a rupture had taken place, or was taking place. Harbitz[7] found a similar condition in 20 per cent. of the children mentioned in his work. There is no reason to believe that a similar rupture may not take place in the adult. It is impossible always to locate such points of rupture at the necropsy for the simple reason that so many of these patients are sick over a period of years, by which time the traces of what occurred in the beginning have been practically eradicated. In acute, rapidly advancing tuberculosis, however, one may occasionally find such a point of rupture. This was our experience recently, and proved to our minds, at least, that such a rupture may occur in adults and may be the source of the individual's reinfection. The pathologic anatomist has not been able to demonstrate these things to us as often as he should, partly because he has not searched for the evidence of

7. Harbitz, F.: Untersuchungen über die Häufigkeit, Localization, und Ausbreitungswege der Tuberculose, Christiania, 1905.

such a rupture, and partly for the reason mentioned above. I feel that an attempt to study such things at the necropsy table in the average case of chronic phthisis is just as logical as to put blood hounds on the trail of a murderer weeks or months after the murder has been committed and after the neighboring population has wandered about the scene in such a way as to obscure any traces of the culprit.

Tendeloo[8] has made a very careful study of the mechanical forces operating in the thorax. He shows that the lateral parts of the chest

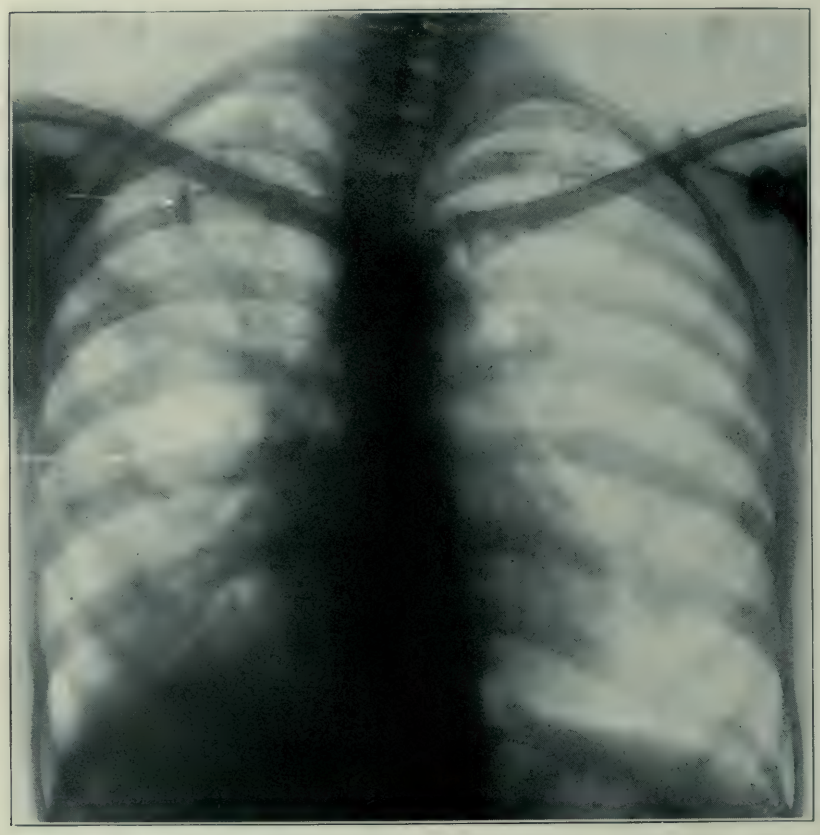


Fig. 4.—Phthisis pulmonalis, three weeks after beginning of symptoms. Arrows point to large cavities. There are scattered infiltrations through both lungs. Patient died three months after date of onset of symptoms.

move the most in respiration. The flow of blood and lymph is most rapid in the lower portion of the chest and the amount of dust or other material aspirated is greatest in these portions. The classical work of

8. Tendeloo, N. Ph.: Studien über die Ursachen der Lungentuberculose, Wiesbaden, 1902.

Arnold[9] on dust inhalation is the best proof of this. One would naturally expect tuberculous material which is discharged from a ruptured gland to lodge most commonly in the lower part of the lungs and produce basal pneumonia. Fortunately, however, the cleaning process of these parts is great also in proportion to the range of mobility. The action of the cilia, along with the bronchial peristalsis, operates automatically to clean those parts. One must not forget that the trachea is fixed at its bifurcation. The descent of the diaphragm on inspiration can stretch those parts of the bronchi that lie below the hilus. The stretching and contraction unquestionably serve to accelerate the cleaning process. Otherwise we would find most of our bronchopneumonias at the bases. It is significant that these aspirations, which result in larger or smaller bronchopneumonias, are almost always above the level of the hilus, which brings them back of the first, second or third interspace. Deformities of the chest which interfere with the movements of the lower part of the chest, such as large intra-abdominal tumors, or deformities of the chest wall itself, readily facilitate the lodging of tuberculous material in the bases, as Tendeloo points out.

If this tuberculous material is aspirated, one naturally asks how it can get to the extreme apices, which move scarcely at all in ordinary respiration or even on forced breathing. I can see only one method by which these apices may become infected. On coughing, there is a tremendous increase of intrathoracic pressure, caused by contraction of all the accessory muscles of expiration, the abdominal and intercostal muscles, along with the closing of the glottis. The pressure exerted equally on all sides of the thorax could not force tuberculous material anywhere except into a part which did not have such support and could yield to such pressure. The only part that does not have firm support on forced expiration is the extreme tip of the lung, which projects through the upper thoracic aperture. All physicians are familiar with the enormous inflation of the apices observed in emphysematous individuals by an increase of the intrathoracic pressure. The elasticity of the pulmonary tissues will permit of a slight degree of inflation which would not be noticed on ordinary inspection of an individual that has no emphysema in these parts. Tuberculous material, which may accidentally be at the mouth of the bronchus leading to the apex at the time of such an increased intrathoracic pressure, can readily be forced up this bronchus into the apex. On account of the lack of mobility of the apices, the cleaning process is very sluggish, and it is comparatively easy for such material, if it is at all tenacious, to lodge there permanently, giving rise to the bronchopneumonic process.

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9. Arnold, J.: Untersuchungen über Staubinhalation und Staubmetastase, Leipzig, 1885.

I am convinced that often material discharged from a ruptured bronchial gland is discharged to the outside, with no disastrous effects to the individual. Probably if we could carefully search the sputum raised by persons who are run down in general health and have slight bronchitis, we would occasionally find tubercle bacilli, which would disappear within a short time. As already mentioned, we have run across one such case in this institution. This aspirated material need not cause a tuberculous bronchopneumonia, but may be expelled after a few days without leaving any marked pulmonary changes behind. We know that this is often the case following large pulmonary hemor-



Fig. 5.—Phthisis pulmonalis. Note three fairly distinct bronchopneumonic areas as indicated by the arrows.

rhages. The factors that control this are in part the normal cleaning process of the bronchi; that is, the movements of the cilia and the bronchial peristalsis, and, on the other hand, the tenacity of the material aspirated. Possibly also the degree of hypersensitiveness of the fixed tissue cells has its influence.

The history of a typical case of phthisis pulmonalis in which the patient has been seen early will usually show a period of sometimes

several months during which there has been a lowered general resistance, progressive loss of weight, perhaps dry, hacking cough, slight afternoon fever, occasional nightsweats, and now and then dull aching pains described under the symptoms of the bronchial gland tuberculosis of the adult. Sometimes these patients will raise mucoid sputum which may or may not be blood tinged. Then later there comes a period, usually lasting only a comparatively short time, that is, from ten days to two or three weeks, during which the constitutional symptoms are much more severe, but still without any marked pulmonary symptoms. Then a patient will begin to raise thick, yellow sputum, and there will be a diminution in the intensity of the constitutional symptoms. Sometimes a patient's actual expectoration will begin with a hemorrhage. These patients do not commonly give a history of exposure to tuberculous infection immediately or within a year or two preceding the outbreak of their disease.

During the stage in which these patients have no pulmonary symptoms, only the constitutional symptoms, the physical examination may reveal only the signs of bronchial gland tuberculosis. These signs may be so slight, however, that even the most expert examination will not detect them. Later, after the pulmonary symptoms have become established, the well known signs of consolidation with softening and possibly cavity formation are apparent. This explains why such a patient will often pass through the hands of several physicians who are unable to make a positive diagnosis, and then, following the hemorrhage, with the purulent expectoration, goes to the "lung specialist," who finds evidences of pronounced pulmonary disease. The lung specialist then, naturally enough, will wonder why the other men who have seen the patient did not make a diagnosis. And one cannot blame him for thinking that these other men know exceedingly little about chest examinations. In these cases one does not have to have recourse to the more subtle physical signs and symptoms to arrive at a diagnosis. Careful percussion and auscultation are sufficient to disclose the lesion. I have sometimes found it advisable, and recommend it as a routine procedure, carefully to search the upper axillary region, which ordinarily is covered by the shoulder cap with its well developed musculature. By having the patient raise his arm above his head one can get at the lateral surface of the chest in the first and second interspace, and it is there that one will occasionally find the only signs of early consumption. This disease does not of necessity attack the apices first, but is usually located back of the first or second interpsace, and quite often laterally under the shoulder cap, where it may escape detection. As stated above, the apices are often infected secondarily, and not primarily, in phthisis pulmonalis.

The laboratory findings before the tubercle is ruptured are the same as those in bronchial gland tuberculosis. After the tubercle has ruptured the sputum will show albumin, elastic fibers and tubercle bacilli as well as the cellular debris which is cast off from such sequestra. Again, there may or may not be a positive tuberculosis complement fixation. During the acute stage, before the rupture of the focus, the urine may show a positive diazo or urochromogen reaction, or both, which disappear when the constitutional symptoms subside. On

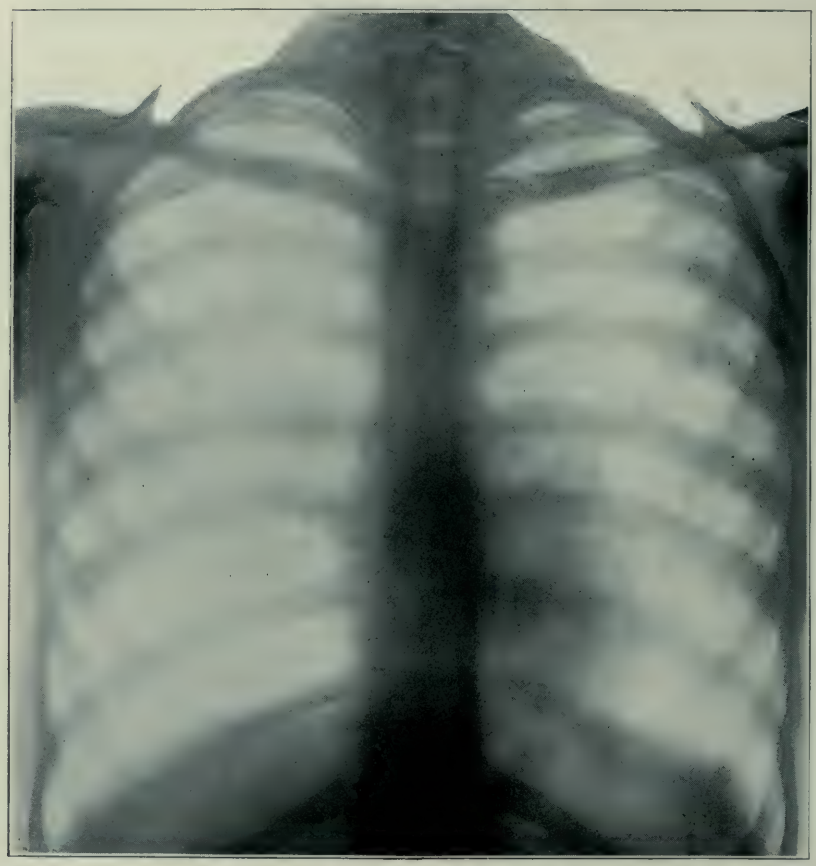


Fig. 6.—Phthisis pulmonalis of seven weeks' duration, according to the history. Note the scattered infiltrations throughout the entire left lung.

account of the gastro-intestinal disturbance, which is usually a part of the constitutional picture, one is apt to find an increase in the indican in the urine.

The roentgenogram reveals a soft, poorly defined shadow, usually above the hilus, back of the first or second interspace, sometimes back

of the third, most often unilateral, although possibly also bilateral. In the mild cases these bronchopneumonias are not very large, but in severer cases, even when found early, may be quite extensive. The apices are very often clear, although occasionally one will find a similar bronchopneumonic process at the apex. The shadows from these early lesions are usually soft, and have been compared to cigaret smoke in appearance. Later, after such a lesion has broken down and discharged its contents, one can readily define a cavity, the size of which will depend on the original bronchopneumonia. When viewed on stereoscopic plates, these soft shadows are broader at the periphery of the lung and point towards the hilus, where one can also notice the shadow of the bronchial wall ending in the apex of such a cone or fan-shaped area. The rapidity with which the lesion may break down and leave a cavity varies in individuals, sometimes occurring quite promptly and in other instances very slowly. What factors control this breaking down we do not know as yet.

PLEURAL TUBERCULOSIS

Genetically, pleural tuberculosis, as we encounter it clinically, belongs in the same class as phthisis pulmonalis, but the clinical picture is sufficiently different from the other types of tuberculosis to warrant its special discussion. Pleural tuberculosis is caused by the aspiration of tuberculous material into the end of a small bronchus which terminates just beneath the pleura. After the tubercle has formed, it may rupture into the pleura instead of into the bronchus and discharge its contents into the pleural space. This is apt to be accompanied by more or less effusion, which may remain clear even though animal inoculation will show tubercle bacilli. In other cases it becomes purulent, due probably to the fact that the dosage of bacilli is greater than in the case with the serous effusion. It is not impossible that this pleura and pleural fluid may have some bactericidal action which makes the pleural tuberculosis often a mild disease compared with phthisis. One does not usually get a pneumothorax along with such a rupture, for the reason that there is no communication between the inside of this tubercle and the bronchi which would permit air to get into the pleural space. Should this tuberculous focus remain for a long period without rupturing, there is a possibility of pleural adhesions being formed at this point, which would make the rupture into the pleural space impossible.

In the primary tuberculosis of children the lesion may be close to the surface of the lung, but effusion in these children from the primary lesion is quite rare. One usually gets a circumscribed dry pleurisy which may cause very little symptomatology. The pleural tuberculosis of adults is, however, metastatic from a ruptured bronchial gland. This explains why these pleurisies are so often in the lower axillary region

where the aspiratory forces are the greatest. The history of such a case will usually demonstrate a period of weeks or months during which the typical symptoms of bronchial gland tuberculosis existed. At the time when the tubercle ruptures and the pleura becomes infected, there may or may not be pain, but there is apt to be a tremendous increase in the constitutional symptoms, which continue for a week or several weeks after the advent of the fluid. During this time there is apt to be irritating cough, with little expectoration, which is usually mucoid in character. If at the same time there are other lesions which discharge their contents into the bronchi, this expectoration may be purulent and contain the usual findings as noted in the sputum under phthisis pulmonalis.

On physical examination the signs of fluid are apparent, and exploratory puncture confirms the diagnosis. In atypical cases the signs are sometimes confusing, due to the fact that there may be points at which the lung is adherent to the chest wall and the breath sounds come through quite distinctly. If the effusion is large, there may be some displacement of the mediastinum, with partial compression of the other lung, which will then show medium coarse, moist, bronchitic râles. Percussion over the uncompressed portion of the lungs is apt to give a tympanitic note (Tabora[10]), and here also one will get some râles that are caused by partial atelectasis.

The roentgenogram presents simply a dense, even shadow which is apt to be triangular in shape, the apex pointing upwards and the base resting on the diaphragm. The remainder of the lung, which is more or less compressed or collapsed, will give indistinct markings and be rather hazy without any actual pulmonary disease necessarily being present.

LYMPHANGITIS TUBERCULOSA

Still another type of intrathoracic tuberculous disease is one which is quite different anatomically from any of the foregoing and is characterized by an extension of the tuberculosis by continuity along the lymph channels from an existing bronchial gland focus.[11] This type of tuberculosis is accompanied by a great amount of connective tissue proliferation, with a gradual fibrosis of the parts involved. The condition progresses very slowly. The first extension from the bronchial glands takes place toward the apices, and especially toward the posterior, paravertebral parts of the lungs. It is difficult to say whether or not the cause of this extension is primarily a stopping of the lymph drainage into these glands, due to the glandular disease, which would permit extension along these channels in a direction naturally contrary

10. Tabora: München. med. Wchnschr., 1904, **51,** 2327.
11. Nicol, C.: Beitr. z. Klin. der Tuberk., 1914, **30,** 2.

to the lymph stream. According to the common conception of the spreading of tuberculous disease, it does not spread against the stream of any body fluid, but rather in the direction of this stream. It is difficult to say just why in certain cases such an extension takes place and in other cases does not. It is probable that in many cases of tuberculous disease of the bronchial glands a certain amount of this extension takes place. The important feature of this form of tuberculosis is that it is interstitial, in direct contrast to the intra-alveolar phthisis pulmonalis. It is of course possible that in some cases the interstitial disease may break through into the alveoli. If the disease once breaks into the alveoli and tubercle bacilli are liberated into the bronchi, one may never tell into what healthy parts of the lung these organisms may be

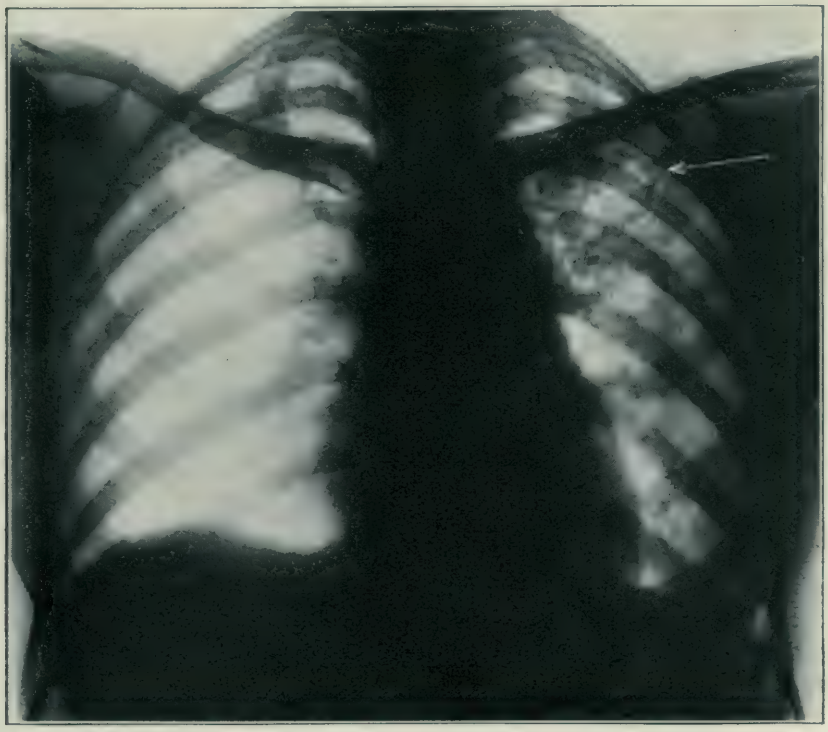


Fig. 7.—Lymphangitis tuberculosa of the right apex, with a possible bronchiectatic cavity. Throughout remainder of the lung, scattered small consolidations.

aspirated. It is easily possible that such a breaking through into the alveoli may result in the beginning of an intra-alveolar phthisis pulmonalis. Bronchiectases are not uncommonly found in the parts of the lungs affected with this interstitial type of tuberculosis. This is the true infectious granuloma, in contrast to the destructive tuberculosis

found in various parts of the body. It is not, however, a common type of disease, at least in our experience. It makes itself apparent clinically first of all at the apices, and then, unless the progress is arrested, spreads from the apices slowly downward until there is sufficient involvement to cause death.

The case history of a patient suffering with lymphangitis ascendens tuberculosa will show a very gradual onset, with mild constitutional symptoms, which slowly get worse, and with comparatively few pulmonary symptoms. Here again the history of exposure to tuberculous infection may or may not be obtainable and the disease may manifest itself following a period of overwork or excessive strain on the body forces. The pulmonary symptoms themselves are usually a slight hacking cough, with little or no expectoration, although occasionally the sputum may show slight streaks of blood. There is apt to be unstable pulse and slight evening elevation of temperature. There may be gastro-intestinal symptoms, which are caused by the toxemia. Some of these patients will complain of rheumatic pains about the shoulder, and I have seen one case in which the typical Poncet's disease existed. These pains do not yield readily to salicylates, are affected by barometric changes, and, on the other hand, are in no way similar to the pains of acute metastatic arthritides.

The physical examination shows diminished resonance over the upper part of one or both lungs. The percussion note never shows the marked changes one notices in pneumonic consolidation. There may or may not be accentuation of the supraclavicular and infraclavicular fossae, although sometimes these patients on inspection show a marked degree of contraction in that part of the chest overlying the disease. On auscultation the change of breath sounds may be only slight or quite pronounced, and the râles are usually medium and fine and moist. Signs of cavitation are absent of course. If the disease is unilateral there may be displacement of the trachea towards the diseased side, and, when the disease is extensive, displacement of the heart is found. On observation the signs of activity in such lungs may diminish very promptly under treatment. I have seen cases, however, in which, in spite of the disappearance of moisture from the lung, the instability of pulse and temperature remained, and there was not the improvement in the patient's general condition that one would expect.

The laboratory examinations usually show sputum negative for tubercle bacilli, containing only the usual mouth organisms and cells. Tubercle bacilli may, however, occasionally be found, only to be absent at subsequent examinations. Elastic fibers will of course be absent from such a sputum. Usually the sputum is so small in amount that the test for albumin cannot be made, or is omitted because of the apparent lack of severity of the disease. The urine will not show

diazo or urochromogen reactions, unless some acute process becomes engrafted on the one already existing, when there is apt to be an increase in the amount of indican present; otherwise the urine findings will be negative. The blood may or may not show positive tuberculosis complement fixation. We have had too few such cases to make extensive laboratory study of them.

The roentgenographic picture is quite distinctive and shows greatly increased peribronchial markings extending from the hilus to the periphery. These markings are not smooth, but irregular in density and show some nodulation. There may or may not be an outline of bronchiectatic cavities in such lungs, which are to be distinguished from ordinary tuberculous cavities, in that they are quite long compared to the breadth, and their direction is always toward the hilus. One always notices marked bronchial gland involvement.

The clinical pictures described thus far have been taken from clear cut cases of the different types of tuberculosis. I do not wish to be understood as claiming that every case of tuberculosis must coincide with one of these descriptions of a certain type. We often have a number of different forms of tuberculosis present at the same time, with, however, one or the other general type predominating.

MILIARY TUBERCULOSIS

The genesis of miliary tuberculosis is too well known to require any comment. I mention it in connection with this paper for the reason that its pulmonary manifestations are often a great aid in the diagnosis. Miliary tuberculosis may be a general miliary process, or, in some cases, if the number of bacilli that get into the blood stream is small, one may only have a metastatic tuberculosis in some bone, joint, the kidneys, the brain or meninges. The bronchial glands are not uncommonly the point from which these hematogenous metastases take place. Whether one gets a general miliary infection with its fatal result, or an isolated metastatic process, the genesis is the same. I believe that the dosage of organisms that get into the circulation is one of the most important features in determining whether there will be a general miliary or an isolated metastatic process. No doubt also the resistance of the individual, whether one considers that resistance is the general condition, or a state of immunity, or both, plays an important part.

In these cases one occasionally may observe a similar picture to that which Roemer reports in some of his experiments on sheep. He found that in sheep which had an existing tuberculosis and were then inoculated intravenously with ten times the fatal dose of bovine tubercle bacilli, there was an immediate temperature reaction and probably also a marked constitutional reaction. This temperature elevation slowly

diminished, until at the end of two weeks it had reached the normal and the animal remained entirely well. In the control, nonimmunized animals there was no immediate reaction and the temperature began to rise after several days, until at the end of two weeks it had reached the level obtained immediately in the immunized animals. It would then remain at that level until the death of the animal. In human beings the onset of abortive miliary tuberculosis may be accompanied by the same type of fever reaction as in the sheep; whereas in other cases in which no immunity exists the temperature will gradually rise and then remain high as in the nonimmunized sheep. It is of importance to bear these things in mind in placing value on the temperature curve of a suspected case of miliary tuberculosis.

Inasmuch as I can bring nothing new concerning the diagnosis of miliary tuberculosis, I will not discuss the physical findings or the laboratory findings in this disease. It may be well to lay stress on the value of the Roentgen ray in the diagnosis of pulmonary miliary tuberculosis, which is the best means we have at our command for making such a diagnosis.

CONCLUSIONS

1. The primary tuberculosis of children is the result of direct inoculation by inhalation of either dried bacilli or droplets containing bacilli. The primary lesion is usually small and very often near the surface of the lung. The regional bronchial gland involvement is invariably present, and the symptomatology is caused by the bronchial gland disease.

2. The bronchial gland tuberculosis of the adult may be a flaring up of a latent process which dates back to childhood, or may be the result of the infection of an adult who has never before come in contact with tuberculosis. Here again the symptoms are caused by the glandular disease.

3. Phthisis pulmonalis is a bronchogenic metastasis from a diseased gland. In rare instances it may be caused by the reinfection from without of an already infected individual.

4. Pleural tuberculosis, as we know it clinically, either dry or with effusion, is also a metastasis from a preexisting focus in a bronchial gland or in the lungs themselves. Possibly this may in rare instances be caused by a reinfection from without.

5. Miliary tuberculosis is a hematogenous metastasis which also very often comes from a bronchial gland. This hematogenous metastasis may be such as to result in a general miliary tuberculosis, or in an abortive miliary tuberculosis with local manifestations in the kidneys, joints, etc.

6. Lymphangitis tuberculosa as a clinical entity is a rather uncommon condition, in our experience, and is the true tuberculous granuloma

of the lungs, and presents a very different type of disease than any of the others. It is usually benign, with a good prognosis.

In many instances — we might say, in the majority of instances — tuberculosis is a cryptogenic disease, and the organic manifestations are due to bronchogenic or hematogenous metastasis. From the standpoint of therapy it is of immense importance, just as in other cryptogenic processes, to discover the crypts and use such treatment as will inhibit metastasis, rather than try to treat the metastatic disease after it has once manifested itself. Particular stress should be laid on the diagnosis of bronchial gland tuberculosis before the development of metastasis with its very uncertain outcome.

This work is based on material which is different, possibly, from that observed in sanatoriums which receive patients from higher social strata. The conclusions, however, I believe, will hold good for the material to be found in the average municipal, county or state hospitals and dispensaries.

Municipal Tuberculosis Sanitarium.

THE STUDY OF A SMALL OUTBREAK OF POLIOMYELITIS IN AN APARTMENT HOUSE, OCCURRING IN THE COURSE OF AN EPIDEMIC IN A LARGE CITY*

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The paper which follows gives the results of a study of a small outbreak of poliomyelitis occurring between Sept. 15 and Oct. 1, 1916, in a large apartment house, occupied by thirty families, situated in the outskirts of a large city. Wickman[1] pointed out that the outbreaks of poliomyelitis in the small Swedish villages were the most fruitful sources of knowledge concerning the mode of transmission of the disease. The outbreak of poliomyelitis in the X house seemed to offer in a similar way an exceptional opportunity for study, for the children in it formed a small community of their own, fairly well isolated from the rest of the city.

The outbreak of poliomyelitis at the X house is, however, interesting apart from the standpoint of its epidemiology; for of the 8, possibly 10, children affected, all but 2 escaped paralysis; several furnished unusually good indications of the incubation period; 2 were remarkably fine examples of the "abortive" and 1 of the "masked" form of the disease; moreover, 3 had negative spinal fluid findings, and finally, all 5 children in one family were affected.

The five children in this family, the B family,[2] were under our care; the three children of the A and C families were not seen by us during their acute illnesses, but the physicians who attended them very kindly reviewed their illnesses with us, and the parents, particularly of the A family, were extraordinarily cooperative in supplying information. Our knowledge concerning the illnesses of two children who were taken sick coincidently with the other children, one in the D, the other in the F family, was of necessity derived from indirect sources, the reason for which will be explained later, and was too meager to permit the positive conclusion that the cases were those of

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1. Wickman, Ivan: Acute Poliomyelitis (Heine-Medin's Disease), 1913. Translated by J. W. J. A. M. Maloney, Monograph 16, Nervous and Mental Disease Series, New York.

2. In the presentation the families will be designated as A, B, C, D, etc., the children by fictitious first names.

poliomyelitis, though we felt very strongly that one of them, at least, was that disease.

At the time of the outbreak of poliomyelitis at the X House, the epidemic in the city, which had begun July 5 and ended December 1, was at its height. Previous to the development of the first case in the X House, 85 cases of poliomyelitis had been reported, and following it there were 120 additional cases, making a total of 205 (almost all of these were of the paralytic type) in a population of about 600,000.



A map of the city. The black dots, squares and oblongs represent the location of cases of poliomyelitis in the city up to the outbreak of the disease in the X House. The location of the X House is indicated by X at upper part of the map.

The mortality (from the reported cases of the disease) was in the neighborhood of 33 per cent. (see map).

The X House is a large, modern, five-story apartment house, containing thirty suites, situated in the northern part of the city, about 3 miles from its center and bordering on one of the most fashionable residential suburbs. Though it fronts on a broad avenue, it occupies

a fairly isolated position, for across the avenue, as well as on the other three sides, for some little distance, there are open fields. The house is provided with all modern conveniences. The sewage disposal system connects with that of the city. The water is also derived from the city supply, although the drinking water used by the majority of the families in the house was obtained from a spring in the immediate neighborhood. There is no public dining room. The families living in the house obtained their groceries and meats chiefly from a store in the neighborhood, though to a considerable extent also from the stores and markets in the central parts of the city; their milk from the various dairies of the city and their ice from a common source.

The thirty families which occupied the house consisted at the time of the outbreak of about seventy adults and eighteen children, the latter varying in age from infancy to 13 years. So far as the children were concerned, it may be said that they formed a society of their own, playing with each other in and about the house, not often going elsewhere or receiving visitors from without. But it was evident that the little community of children was isolated only in a comparative sense, for plenty of lines of communication with the outside world remained open, along which the infection might have found its way to them.

Although all the children in the X House inevitably came into contact with each other, since they lived in the same building and shared a common playground, yet on account of differences or similarities in age and taste, and for various other reasons, some had little or nothing to do with the rest, while others moved in small groups or cliques. Maude S, Nancy H, Jenny J, Fritzie H and J. N. (a boy who used to come from the city to play) were older and had little to do with the others. William S, who seems to have been *persona non grata,* usually remained alone with his nurse, and Dick E was purposely kept from the others by his parents. Baby B and Baby A were infants in arms. The remaining eleven children were also more or less subdivided into twos and threes. Jack C and Elizabeth D were inseparable; Fritzie H and Charlie B were almost constantly together, etc. The four older B children and the two C children, on the other hand, played little with each other and did not go to each other's apartments, and Ned F did not have much to do with the B's, but sometimes played with the C's. But all of these eleven children had this in common, that they were on especially friendly terms with the A children and frequently visited the A's apartment. In this sense it is possible to divide the children in the X House into two groups, the one group visiting the A's apartment and centering about A's, the other group not having these relations.

The A's apartment, situated on the ground floor of the X House, was readily accessible from the lawn. Mrs. A was exceptionally kind

to the children and gave them butter-bread or wafers when they came even to the door, and her own children were especially popular, with the result that the A's apartment and back porch became a favorite rendezvous. Ned F, the great friend of Harry A, used to "spend his entire time there"; the B children, except the baby, were very frequent visitors *en masse*, and often the two C children and Nancy H used to come. The A children had many toys — dolls, stuffed monkeys, Teddy bears, balls, tin horns, scissors for cutting paper dolls, etc. — and allowed all the visiting children to use them, so that the toys passed from one to the other, and were, in the A's apartment, common property. The games that were played were the games of children everywhere. It should be mentioned, however, that on the lawn there was a sandbox, about 8 by 8 feet, which was used by almost all the children in the X House, even by the older children; Dick E and William S used to be taken there when the others were not present.

Sept. 15, 1916, the case which we regard as the first of infantile paralysis made its appearance among the children in the X House. On the evening of this day, Harry A, aged 2½ years, was taken ill. September 11, five days previously, both he and his sister, Barbara A, 3½ years old, had what their parents regarded as a "digestive upset," accompanied by rather high fever. But both children were so much better on the following day after castor oil that they were considered well again. Harry A remained in normal health from that time until the beginning of his acute illness, five days later. He went to bed to all appearances perfectly well, but was found at 11 o'clock, screaming with pain. He was nauseated and vomited. His temperature was 103 F.[3] All night he was extremely restless, slept fitfully and frequently cried out. The next day, September 16, he seemed extremely ill. His temperature was 103. The parents now noted something never seen in any of his previous illnesses and remarked on it at the time as being strange: that he cried whenever touched or moved, and put his hand frequently against the back of his neck. At times he seemed "out of his head." September 17, the third day of his illness, he was seen by the family physician, who was said to have made a very casual examination, and who left the impression that the illness might be a "bilious attack" or "malaria" (no blood examination was made). His temperature was then 102 F. The sensitiveness to touch continued. For the next three days Harry A remained in bed (or on a couch in the living room), except twice, when taken out for a drive. On the fourth day his temperature began to fall and his condition steadily improved. During this time the parents observed that, when he was taken out of bed, he was unable to climb back into it, and that he could get on his hands and knees but had difficulty in sitting up. When Harry A was strong enough to walk the parents became troubled at his way of doing it, and on September 23, the eighth day of his illness, made him walk before Mr. B, in order to obtain the latter's opinion. September 24, the ninth day of his illness, they consulted their physician, who, however, did not find anything wrong (according to the parents he did not test the child's reflexes). After that time the little boy rapidly recovered his former strength and is now perfectly well, except that he becomes fatigued easily when walking. Apparently the possibility of poliomyelitis was not suspected, and no physical examination with that in mind was made.

Either on the day following Harry A's illness or two days later (Mrs. A does not remember which) Baby A, aged 4½ months, developed a fever of

3. All temperatures are mouth, except in the case of Baby B, which are rectal.

103 F., and vomited. She is said not to have had fever previously but to have been subject to indigestion from birth, was malnourished and vomited frequently. Her temperature did not become normal for ten days. The baby was not seen by a physician.

Barbara A remained well during this time.

Illness next appeared in the B family, which consisted of Mr. and Mrs. B, a foreign white maid and five children. They lived on the ground floor of the X House. Mr. B used to go in the street cars each day to his laboratory in the city, where, however, he was not exposed to poliomyelitis or any other disease. Mrs. B and the maid, who spoke no English, remained at home practically the entire time. All three were in perfect health during the month which preceded the children's illnesses. They had one guest during the summer, but he had left more than a month previously. It is an interesting fact, as possibly indicating a predisposition to poliomyelitis in the B family, that one of Mrs. B's sisters and one of her cousins are paralyzed as the result of poliomyelitis in infancy.

As already mentioned, the children of the B family were particularly intimate with the children of the A family, and frequently visited the latter. September 16, the second day of Harry A's illness, Bobby B went to see Harry A and spent the entire morning playing with toys in the A's apartment. On the following day, September 17, Charlie B twice brought broth for Harry A and was in the A's apartment a half hour. He "caressed" Harry A but did not kiss him. On the following day or the day after, either September 18 or 19, the parents cannot remember which, Charlie B, Dorothy B and Mary B visited the A's apartment in order to see Harry A, and spent a half hour or more playing, and while there received buttered toast prepared for them by Mrs. A. It is thus seen that the contact between the B children, with the exception of the B baby, and the A children during Harry A's illness is very definite. The exception of the B baby to this contact is important, because the B baby was the only one of the B children who, within the nine days following the onset of Harry A's illness, did not contract poliomyelitis. For the two weeks previous to their illnesses the B family were not exposed, to their knowledge, to any sick person with the exception of Harry A and Baby A.

September 21, five days after the onset of Harry A's illness, Bobby B, aged 6½ years, was taken sick. That morning he had eaten a good breakfast and had been roller-skating for two hours, when he came into the house complaining that he felt sick and his head ached. His temperature was found to be 103 F. He went to bed seeming "a little dull," and refused dinner, but got up in the afternoon in order to see his teacher. He had a poor appetite for supper, and went to bed again immediately afterward. The next morning, September 22, he seemed so much better that his parents did not think it necessary to take his temperature and regarded him as being practically well. After a rather poor breakfast he went out of doors and remained there almost the entire day, the greater part of which he spent in roller-skating, coming in only for his dinner. Though he did not seem actually sick, he looked pale and did not act like himself. He went to bed without eating supper. The following day, September 23, he ate a good breakfast and went out roller-skating again, but returned at 11:30 looking very ill. It seemed to his parents that a sudden change had taken place; his temperature was 103 F., and he again complained of severe headache. He was put to bed at once and soon became so drowsy that it was necessary "to shout" to get an answer. He now began to complain of pain in the back of his neck and in the front of his head, and at 7 in the evening he vomited. The following day, September 24, he seemed slightly better and no longer complained of headache, and played with paper dolls. His temperature was 102.5 F. When seen late that afternoon by one of us, he was in bed, rational, and did not complain of pain, but looked extremely sick and exhibited the restless behavior of children with a high fever, though his temperature was only 102.5 His face underwent

frequent choreiform-like contractions. Some nasal obstruction was present, but unaccompanied by discharge. The knee and ankle jerks were exaggerated. No clonus was present. On attempting to obtain the Kernig sign, marked pain was elicited. There was general hyperesthesia; otherwise the physical examination was negative. That evening he became much worse, complaining of pain everywhere, and evidently paralysis had begun to manifest itself, for he could not stand. The following morning, September 25, he was again seen by one of us. His legs were almost completely paralyzed, though some slight motion of the left great toe was still present. Knee and ankle jerks were now absent. The diaphragm seemed to be completely paralyzed and thoracic respiration was feeble. Each inspiratory movement was accompanied by marked dilatation of the nostrils and gasping movements of the mouth. Slight internal strabismus had appeared and the left pupil was smaller than the right. About 1:30 p. m. there was a general convulsion. From this time on respiration was kept up by means of a "pulmotor." He was transferred to the poliomyelitis hospital. On arrival, spinal fluid was obtained, which showed 250 cells and a positive reaction for globulin. He was given 10 c.c. of immune serum intraspinally. He died at 1:30 the following morning.

At necropsy the typical lesions of acute poliomyelitis were found. There was a general lymphatic hyperplasia, most marked in the solitary nodule of the large and small intestines, Peyer's patches, and the mesenteric lymph nodes. The brain was soft and congested. The pons, medulla and spinal cord were swollen and edematous. There was a sterile fibrinopurulent exudate over the surface of the spinal cord (injection of immune serum). Microscopic examination showed hyperemia; extensive perivascular and diffuse infiltration of cells, mostly mononuclear, nerve cell degeneration and neurophagocytosis in the tegmenta of the pons and the medulla, and especially the anterior horns of the entire cord.

September 23, two days after Bobby B was first taken sick, at about 10 o'clock in the evening, it was noticed that Mary B, aged 2½ years, did not seem well. The next morning, September 24, her temperature, taken for the first time, proved to be 103 F. Since her parents found it difficult to keep her in bed, they dressed her and allowed her to sit or wander about the house throughout the day. When seen by one of us in the late afternoon of September 24, her temperature was 102.5. She looked pale but did not act especially sick, did not complain, and gave no indication of headache. No examination was then made except to determine that both knee jerks were present but not active, that no paralysis existed and that her throat was clear. Her gait was normal. The next day, September 25, she seemed somewhat better, but was removed to the poliomyelitis hospital. On her arrival there she was very drowsy and irritable when disturbed; her temperature, however, was 99. Physical examination revealed nothing. A spinal puncture was made; the fluid obtained contained a trace of globulin but only five cells per cubic millimeter. (The physician who made the puncture is certain that there was no admixture of blood).

Three days after the beginning of Bobby B's illness and on the day following the illness of Mary B, namely, September 24, Charlie B, aged 9½ years, was suddenly taken ill. Charlie B had eaten a fairly large breakfast that morning and had been out of doors playing, but returned to the house about noon, complaining of severe headache. His temperature was 103 F., and he was immediately put to bed. When seen late that afternoon by one of us his temperature was still 103; his face was flushed. He lay in bed, appearing in great distress, with his hand pressed against his forehead. He continually tossed about and his face twitched. On examination it was noted that the knee jerks were hyperactive; well marked hyperesthesia was present, and flexion of the extended leg in the attempt to obtain Kernig's sign seemed to produce a great deal of pain. The neck was not stiff, and in other respects the physical examination was entirely negative. On the morning of the next day, September 25, the temperature was 102 but his condition was greatly improved. He was found

sitting up in bed, cutting out paper dolls, and said his headache had entirely disappeared. A leukocyte count taken at this time showed 19,000 white blood cells. The physical examination was entirely negative, except that the knee jerks were still overactive. That afternoon about 2 o'clock he was transferred to a poliomyelitis hospital with his brother and two sisters. On arrival his temperature was 99.2 and lumbar puncture showed five cells and a negative reaction for globulin. Eight cubic centimeters of immune serum were given, however, intraspinally. The urine contained albumin. The boy quickly recovered his normal condition. A lumbar puncture repeated October 11, seventeen days after the onset of his illness, showed a clear fluid, which gave a negative globulin and contained only two cells to the cubic millimeter.

At 5:30 in the afternoon of September 24, Dorothy B came into the house complaining of headache. She had been out of doors almost the entire day, had eaten her usual dinner, and seemed in customary health. Her bowels had moved normally. Her temperature was immediately taken and found to be 104 F. She was put to bed. Her face was flushed. She seemed to her father very ill. She held her head and complained of headache exactly as her brother Charlie B had done. On the following morning, September 25, she was seen by one of us. A physical examination revealed nothing excepting overactive knee jerks. She was found sitting up in bed and said that her headache was gone. Her temperature was then 102.5. At 2 o'clock in the afternoon she also was taken to the poliomyelitis hospital. On admission her temperature was 101.6; pulse 140. Physical examination was negative. The spinal fluid showed three cells per cubic millimeter, and a negative test for globulin. She was given, however, 10 c.c. of immune serum intraspinally. The following day her temperature was normal. October 11, seventeen days after the onset of her illness, spinal fluid was again obtained; it contained nine cells per cubic millimeter and the test for globulin was negative.

September 24 the illness appeared also in the C family. The C family was composed of Mr. and Mrs. C, Mrs. C's mother and two children, Jack and Billy. At this time they had no servant. Mr. C, a business man, went to his work daily, using the street cars. Mrs. C and her mother had been out of the house very little during the two weeks which preceded Jack C's illness. Neither Mr. C, Mrs. C, nor Mrs. C's mother had been exposed to any illness so far as they were aware, and the children had not been in contact with any sick person except Harry A.

Jack C was 6 years old. About a week before the beginning of his acute illness he had a digestive upset (a frequent occurrence). This kept him in doors until September 21. On that day his physician allowed him to go out. In the morning he and his brother, Billy C, were taken for a half hour's drive by Mrs. A in the governess' pony cart, together with Elizabeth D, Barbara A and Harry A. It was the fifth day of Harry A's illness and he was still so weak that he had to be lifted in and out of the pony cart. Mrs. A, who drove, recalls that Elizabeth D and Barbara A, who were seated in the pony cart next to Harry A, quarreled so much that she removed Elizabeth D, putting Jack C in her place, so that Jack C and Harry A sat next each other for the greater part of the drive. Mrs. A says that the only reason she remembers the incident is that, when Jack C was placed next to Harry A, she noticed that both children looked pale. Mrs. A also says that the pony cart was so small and on this drive so crowded that all the children sat with their heads close together. Jack C was not exposed to any sick person during the two weeks preceding his acute illness except to Harry A on this occasion.

At 2 o'clock in the morning of September 24, the day on which Charlie B and Dorothy B were taken sick, Jack C awoke his parents complaining of headache, and shortly afterward vomited. His parents took it for granted that Jack C was suffering from another of his digestive upsets, but by the next morning, September 25, his condition had become so serious that they called

in their family physician. Jack's temperature was then 102.5 F.; the headache had become more intense and vomiting had recurred a number of times. When the physician arrived he found well-marked rigidity of the neck, increased reflexes, a positive Kernig sign and an extreme degree of hyperesthesia. The boy was extremely drowsy; occasionally he cried out in his sleep and twitched convulsively; at times he was delirious. September 27, the third day of his illness, a lumbar puncture was performed. The spinal fluid was sterile but contained 173 cells to the cubic millimeter, a preponderance of which were polymorphonuclear leukocytes, and the globulin test was faintly positive. At this time his temperature was 102.3 F. In the course of the next three days the temperature fell to normal and all symptoms disappeared. No paralysis developed. For the five weeks which followed he was kept in bed and the family have no idea whether any muscular weakness was present. He is now, January 1, entirely well.

The next child to be taken sick was Ned F, 3 years old. The F family was composed of Mr. and Mrs. F, their only son, Ned, and two servants. For some time Mrs. F and Ned had been at a summer resort which was considered free from poliomyelitis. They had returned to the X House only seven days before Ned became ill. None of the adults in the family had been exposed to any sick person, so far as is known, and were themselves well previous to Ned's illness. Ned F, as will be remembered, was a special friend of Harry A, and during Harry A's illness Ned F was repeatedly in the A's apartment. Mrs. F took Ned F and Harry A for an hour's drive in her automobile on September 20, the fourth day of Harry A's illness. Harry A was so sick at the time that he was carried to and from the automobile. We could not learn that Ned F was exposed to any other sick child than Harry A.

We do not know the exact details of Ned F's illness. Indeed, at first it was denied altogether, and later, only the fact admitted. From other sources we have learned, however, that on September 25, the day on which the B children were removed to the hospital, Ned F was taken sick and vomited. At noon of that day Mrs. F, learning that the B children had infantile paralysis, in great excitement wrapped Ned in a blanket and left the city. She is reported to have said that Ned looked so sick that she could not understand how she succeeded in passing the officials at the railroad station; that he vomited several times that day and night and felt hot; that she was terrified, and that he did not seem well again for ten days. We also learned that Mrs. F said she felt perfectly sure Ned had the disease. At any rate, he did not develop any paralysis and is now well.

On the day on which the B children were removed to the hospital and Ned F was taken sick, Elizabeth D, aged 5, the only daughter of Mr. D, an employee of the X House, became ill. The D family lived in the basement of the X House, and consisted of Elizabeth D, her father and an aunt. We could discover little in regard to her or her family during the two weeks which preceeded her illness. We cannot find that she entered the A's apartment or came in contact with Harry A during his illness except on one occasion, namely, during the half hour's drive in the pony cart on September 21, the fifth day of Harry A's illness. Her boon companion was Jack C, and, if Elizaebth D had poliomyelitis, we should expect to find that her exposure occurred at the same time as that of Jack C (see page 62).

We have very little information in regard to Elizabeth D's illness. Her father denied to us that she was sick at all, but he told at least three of the residents of the X House that she was "very sick" on the night of September 26, and that he was "scared for fear she had infantile paralysis" and, in fact, a resident in the X House informed us that he knew at the time that Elizabeth D was ill, because he was kept awake by her screaming. The doctor who visited Elizabeth D informs us that she had an earache. He did not examine her ear

drum and her ear never discharged. Whatever the nature of her illness, it is certain that she was suddenly taken sick coincidentally with the others.

The next child to become ill was Billy C, aged 4. It will be remembered that Billy C was present, as well as his brother, Jack C, on the drive in the pony cart with Harry A. September 28, four days after Jack C's illness began, Billy C was suddenly taken sick. The evening preceding, the family doctor saw him and testifies that he was in normal health. At 1 o'clock in the morning he awakened his parents complaining that he could not sleep. At 8 o'clock he vomited. His temperature was then between 104 and 105 F. He had no headache but complained of pain in the back of his neck. When seen by the physician, the neck was rigid, the Kernig sign positive; the tendon reflexes were exaggerated; marked general hyperesthesia was present. At times he was delirious. In fact, his illness was more severe than that of his brother. At the end of six days his symptoms had entirely disappeared and no paralysis occurred. He, too, was kept in bed for five weeks, at the end of which time he seemed to have recovered entirely.

Baby B, the only one of the B children who had thus far escaped infection, was a healthy baby, 4½ months old, but weighing only 9 pounds. Her mother used to keep her out of doors on the lawn in a basket for a large part of each day when the weather was pleasant, but had not done so during the nine days which preceded her illness, because of the illness of Bobby B and the other children. Baby B's brothers and sisters came into the closest contact with her, and of the four, Bobby was the most devoted to her, often kissing and caressing her. Dorothy B frequently carried the baby about in her arms, and in the early morning it was the parents' custom to take the baby into their own bed, where the other children gathered to play with her. The parents vividly recall that on September 22, during the intermission which ensued between the acute symptoms of the onset of Bobby B's illness and those which preceded his death, he repeatedly kissed and fondled the baby.

Immediately preceding her acute illness Baby B was perfectly well, except for a slight cold, and did not come in contact with any sick person except her brothers and sisters.

At 6 o'clock in the evening of October 1 the baby was exhibited to a guest, a physician, and gave every sign of being in perfect health. At 10 o'clock Mrs. B observed that the baby's skin felt hot, but did not take her temperature, for lack of a thermometer. The baby took the 10 o'clock feeding well, but afterward seemed very sick, sleeping hardly at all and frequently crying out as if in pain. The parents, alarmed, remained awake the entire night. The following morning, October 2, the baby's temperature was found to be 102.5 F. She was exceedingly restless and very hyperesthetic. Her bowels moved normally and there was no vomiting. Late in the afternoon of October 2, the baby was seen by one of us. She looked very ill, frequently crying out, and screamed when touched. The fontanel was full, the pulsations particularly pronounced. Retraction of the neck was apparent and when the head was flexed on the chest, she screamed, though she did not resist the flexion. The knee jerks were much exaggerated and the ankle jerks easily obtained, but there was no clonus and no Kernig sign. No paralysis was present. A lumbar puncture was twice done and bloody fluid obtained, under apparently normal pressure. That evening the temperature rose to 103.6 F. By the following morning, October 3, the third day of the disease, paralysis had appeared, with involvement of the left deltoid, pectoralis major and triceps muscles. On this day the baby was removed to a poliomyelitis hospital. On arrival a lumbar puncture was performed; the clear fluid obtained contained 270 cells to the cubic millimeter and remained sterile. During the course of the day, weakness developed in the flexor muscles of the left leg. The temperature continued elevated for four days and then fell to normal. The baby still (Jan. 1, 1917) has paralysis of muscles of the left arm.

Thus, of the eleven children who formed the group which came into especially intimate contact with the A family, all but two developed some kind of an illness within a week of each other and within the thirteen days which followed the onset of Harry A's illness. The two who escaped were Barbara A, Harry A's sister, and Fritzie H. Barbara A was, of course, more exposed to infection, provided it centered about her brother or in the A's apartment, than any other child in the X House, and ought under those circumstances to have contracted the disease before any of the others.[4] We cannot find that Fritzie H, on the other hand, entered the A's apartment at all or came in contact with Harry A during his illness, and if exposure in the A's apartment or to Harry was essential for infection, ought to have escaped it. She was exposed, however, to Bobby B on September 22, the day marking the intermission period of his illness, for on that day she was taken on a drive with him and Barbara A in the A's pony cart; but she remained well (Table 1).

EXPERIMENTS

The following experiments were planned with a view to proving that certain of the cases of illness among the children in the X House, not accompanied by paralysis, were poliomyelitis, and in the hope that by the method employed we might be able to trace the outbreak back to its starting point.

EXPERIMENT 1 (*a*).—Oct. 13, 1916. *Ringer solution washings of the nose, mouth, pharynx and intestines of Charlie B, obtained when in perfect health, nineteen days after the onset of his illness; the filtrate injected into a monkey.*

The washings of nose, throat and mouth were made by passing the Ringer solution through these passages several times, until it was rich in mucus. The intestinal washings were obtained in a similar manner, after the fecal matter had been removed by means of a normal saline enema. Both sets of washings were mixed together, shaken and passed through a Berkefeld filter, which would not allow the passage of the *B. violaceus*. Fifty cubic centimeters of filtrate were obtained, 2 c.c. injected into the left lateral ventricle, and 10 c.c. into the peritoneal cavity of *Macacus rhesus* 1, a small monkey which had been in the laboratory about four years. The monkey appeared healthy. The injections were made under ether anesthesia.

This monkey recovered at once and remained well for forty-eight hours. He then showed weakness in his right hind leg, later in his left hind leg, and a prolapse of the rectum developed. He dragged his hind parts. On the fourth day his front legs became weak and his respirations rapid He was unable to lift himself from the floor. He was not, however, completely paralyzed in any of his extremities. On the fifth day his respirations became slow and labored and he died. At necropsy, no lesions of the organs were found excepting hyperplasia of the lymphatic nodules of the spleen, stomach, intestines,

4. It will be remembered that Barbara A was ill on September 11, with a temperature of 104 F. It is possible that she had poliomyelitis at that time, but scarcely probable, because her illness was in no way typical and could be explained on dietetic grounds.

TABLE 1.—Indicating Age and Family Grouping of Children and Exposure to and Incidence of Poliomyelitis Among Them

Children of	Age, Yrs.	Exposure to Harry A or His Immediate Environment	Poliomyelitis	Unexplained Illness Occurring Coincidently with the Cases of Poliomyelitis	No Illness	Outcome Form of Disease
A Family						
Barbara	3½	+[1]	..	..	+	
Harry	2½	..	+	..	..	Recovery; nonparalytic
Baby	⅓[2]	+	..	+[3]	..	Recovery
B Family						
Charlie	9½	+	+	..	..	Recovery; abortive
Dorothy	8½	+	..	..	..	Recovery; abortive
Bobbie	6½	+	+	..	..	Death; ascending paralysis
Mary	2½	+	+	..	..	Recovery; "masked" form
Baby	⅓[2]	—[4]	+	..	..	Recovery with paralysis
C Family						
Jack	6	+	+	..	..	Recovery; nonparalytic form; spinal fluid
Billy	4	+[5]	+	..	..	Recovery; nonparalytic
D Family						
Elizabeth	5	+	..	+[6]	..	Recovery
E Family						
Dick	2	—	..	..	+	
F Family						
Ned	3	+	..	+[7]	..	Recovery
S Family						
Maude	13	—	..	..	+	
William	5	—	..	..	+	
H Family						
Nancy	8	—	..	..	+	
Fritzie	12	—	..	..	+	
J Family						
Jenny	12	—	..	..	+	
N Family						
J N[8]	12	—	..	..	+	

1. See footnote 4.
2. Four and one half months.
3. See pages 59 and 64.
4. But exposure to brothers and sisters; see page 64.
5. See page 65; and to Jack C.
6. See page 63.
7. See page 63.
8. J N does not strictly belong to the group of children in the X House. See page 58.

lungs and lymph glands. The brain appeared normal. The cord was hyperemic but not edematous. There were a few hemorrhages into the cord and medulla, but no cellular infiltration, except in one small area in the floor of the fourth ventricle. A small part of the floor was infiltrated with round cells, and a few of the neighboring veins showed perivascular infiltration. A number of the sensory ganglia were examined, but no lesions were made out. A piece of the cord was taken aseptically and placed in 50 per cent glycerin.

EXPERIMENT 1 (*b*).—Dec. 2, 1916. *Injection of an emulsion in physiologic salt solution of the glycerinated cord of Monkey 1 into Monkey 2, a healthy Macacus rhesus.*

One cubic centimeter was placed in the left lateral ventricle and 4 c.c. in the peritoneal cavity of this monkey.

EXPERIMENT 1 (*c*).—Dec. 12, 1916. *A thick emulsion in physiologic salt solution of another part of the glycerinated cord of Monkey 1, injected into Monkey 5.*

One cubic centimeter of the emulsion was placed in the left lateral ventricle and 1 c.c. in the peritoneal cavity.

Both of these monkeys remained well up to the time of writing, Jan. 22, 1917.

EXPERIMENT 1 (*d*).—Oct. 29, 1916. *Nasal, pharyngeal and intestinal washings again taken from Charlie B and from his sister, Dorothy B, thirty-five days after the onset of their illnesses, and injected into monkeys:*

Nasal and pharyngeal washings of the two children were mixed together, filtered, and 2 c.c. of the filtrate were introduced into the left lateral ventricle and 10 c.c. into the peritoneal cavity of a large, healthy monkey, 4.

The intestinal washings of the two children were kept separate, shaken and filtered and injected in the same manner, each into one of a pair of young healthy *Macacus rhesus* Monkeys 5 and 6. These monkeys were well at the end of six weeks.

EXPERIMENT 2.—Oct. 21, 1916. *Washings of the nasopharynx, mouth and colon of Harry A obtained in manner described in Experiment 1, thirty-six days after the onset of his illness, injected into large Macacus rhesus 3.*

Two cubic centimeters were injected into the left lateral ventricle, 40 c.c. into the peritoneal cavity. The filtrate contained very little mucus. The monkey was reported to have remained well.

DISCUSSION OF EXPERIMENTS

Flexner and Lewis found that the filtrate of an emulsion of the nasal mucous membrane of a monkey having poliomyelitis produced the disease when inoculated into a healthy monkey. Following this experiment a number of investigators, Landsteiner and Levaditi, Leiner and v. Wiesner, Römer, Strauss, Rosenau, Sheppard and Amoss and Gins,[5] attempted to transmit the disease to monkeys by means of a Berkefeld or Chamberland filtrate of material obtained from the nose, pharynx or mouth of patients ill with the disease. All the experiments were negative.

In February, 1911, Osgood and Lucas[6] reported successful transmission of the disease to healthy monkeys by means of a Berkefeld

5. See Kling, Pettersson and Wernstedt (Footnote 7) for references to authors just cited.

6. Osgood and Lucas: Transmission Experiments with the Virus of Poliomyelitis, Jour. Am. Med. Assn., 1911, **56,** 495.

filtrate of an emulsion of the nasal mucous membrane obtained from monkeys dying without other demonstrable infection six weeks and five and one-half months after the acute stage of the disease.

By far the largest number of experiments of this kind were performed by Kling, Petterson and Wernstedt,[7] 1912. They attempted to transmit the disease to monkeys by means of a filtrate of the secretion of the nose, mouth, pharynx, trachea and intestines of persons dead with the disease, acutely ill with it, having recently recovered and having recently been exposed to it, and healthy persons who apparently had no contact with the disease. These investigators report a large number of positive results. The technic they used differed in one important particular from that of their predecessors; instead of a Berkefeld, Chamberland or other filter, they used a Heim, which is more permeable.

In 1913, Flexner, Clark and Frazier[8] washed with normal saline solution the nose, mouth and pharynx of healthy parents of a child sick with the disease. The solution was shaken and passed through a Berkefeld filter. One and a half cubic centimeters were injected into the sciatic nerve and 140 c.c. into the peritoneal cavity of monkeys. They developed typical symptoms, and the authors assert that the cords showed typical and characteristic lesions of the disease.

It is thus seen that the disease has been successfully transmitted from infected human beings to monkeys. But the majority of investigators who have attempted thus to transmit the disease have been unsuccessful. Although Kling, Pettersson and Wernstedt report a large number of positive results, and that a high percentage of their inoculated monkeys showed symptoms certainly strongly suggestive of poliomyelitis, the positive interpretations which they put on the results of many of their experiments are open to criticism, in that they accepted purely degenerative changes in the nervous system as a final criterion for the diagnosis of this disease. In fact, the large number of positive results reported by Kling, Pettersson and Wernstedt are difficult to reconcile with the observations of Flexner and Lewis[9] and other investigators, according to which monkeys frequently fail to become infected, even when an emulsion of the spinal cord of another monkey dead of the disease is used, and further, it is known that

7. Kling, Pettersson and Wernstedt: Investigations on Epidemic Infantile Paralysis. Report from the State Medical Institute of Sweden to the Fifteenth International Congress on Hygiene and Demography, Washington, D. C., 1912. Stockholm, 1912.

8. Flexner, Clarke and Frazier: Epidemic Poliomyelitis, Fourteenth Note: Passive Human Carriers of the Virus of Poliomelitis, Jour. Am. Med. Assn., 1913, **60,** 201.

9. Flexner and Lewis: The Transmission of Epidemic Poliomyelitis to Monkeys, Jour. Am. Med. Assn., 1909, **53,** 1913.

human strains are often less virulent to monkeys than strains that have undergone preliminary passage through monkeys, which are more susceptible to the disease.

Negative results following the inoculation of monkeys with secretions which are supposed to contain the virus of poliomyelitis, mean nothing.

In our experiments the material was obtained three and six weeks after the acute stage of the disease and after the children had been well for some time. No attempt was made to concentrate the material, and the material injected was small in amount.

DISCUSSION OF DIAGNOSIS

The clinical diagnosis of poliomyelitis is ordinarily made when a flaccid paralysis suddenly develops without apparent cause in the course of a short, otherwise unexplained febrile illness, usually marked by symptoms of involvement of the central nervous system, and it receives corroboration if certain fairly characteristic changes also occur in the spinal fluid. The paralysis may be so extraordinarily distinctive in the suddenness of its development and selection of muscle groups as alone to establish the diagnosis, but the constitutional manifestations of the disease are never in themselves sufficient to distinguish it from certain other infections. Under unusual conditions, however, the circumstantial evidence favoring poliomyelitis may be so overwhelming as to justify that diagnosis when only the constitutional symptoms are present; that is, when poliomyelitis is in the community in epidemic form and side by side with the case in question, which cannot be explained otherwise; or when in the same family or house, or among playmates, manifest cases of the disease develop having identical onset and symptoms.

Such were the unusual conditions that obtained in the outbreak at the X House; 8 children living in the same house with definite association proved; all taken abruptly sick, without apparent cause, within fifteen days of each other, 6 of them within eight days of each other; 7 of them obviously having the same disease, as judged by the mode of onset, symptoms and physical signs, and 3 of the 7 proved to have poliomyelitis by the development of paralysis or changes in the spinal fluid.[10]

10. The correspondence in the symptoms shown by these children is most interesting. Harry A, Billy C and Jack C were each suddenly taken ill with high fever, vomiting, pain in the head and in the back of the neck, and hyperesthesia, and were at times irrational. All escaped paralysis. Their illnesses, which lasted five to six days, were so similar that the description of one serves for the other two. No other cause for their illness could be found,

The diagnosis of poliomyelitis in the case of Mary B, who did not show all of the symptoms of the others, depended on circumstantial evidence alone. It will be remembered that her illness was characterized only by fever, pallor and malaise. The onset may have been sudden, headache may have been present, but neither was apparent (she was only 2½ years old). The coincidence of her illness, otherwise unexplained, with the illnesses of her four brothers and sisters, leaves no alternative but to regard the illness as poliomyelitis also.

When we come to the illnesses of Ned F and Elizabeth D, it must be said that the data in our possession are insufficient to permit any positive conclusion. But we feel it is not without significance that these two children were abruptly taken sick, five to seven days after exposure to Harry A (Ned F at least, without apparent cause), and coincidently with the six other children. Elizabeth D's "earache" might have been the violent headache which was so marked a symptom in the other cases. We can form no idea whether the illness of Baby A was poliomyelitis or not.

MODE OF CONVEYANCE OF INFECTION

Although now it is very generally believed that poliomyelitis is an infectious disease, there exists considerable difference of opinion in regard to its mode of conveyance from one person to another. The theory which has received most support from clinical experience and experimental investigations on monkeys is that the infecting material is contained in the discharges of the carrier of the disease and conveyed to the noninfected by direct contact, or through the medium of contaminated objects, such as toys, food, clothing, etc. (Wickman, Kling, Pettersson and Wernstedt, Flexner and others), or possibly through the agency of filth-carrying insects, such as the fly. But others have ascribed the conveyance of infection to blood-sucking insects.

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dietetic or otherwise. The spinal fluid was taken in only one case (Jack C) and in that one case it showed the characteristic changes found in poliomyelitis.

Turning now to the B children, the illnesses of Dorothy, Charlie and Bobby, were absolutely identical up to the third day. The onsets were violent, timed to the half hour, marked by intense headache, high fever, extreme restlessness, hyperesthesia and increased tendon reflexes. After the initial stage the improvement was rapid. On the second and third days Bobby B went out to play. Dorothy and Charlie would have done so at the same period had they been allowed. The only difference in the illnesses of the three children was that Bobby B's symptoms started up again on the third day, while those of Dorothy B and Charlie B ceased altogether. No cause for their illnesses other than poliomyelitis could be discovered. Bobby B died of the ascending type of paralysis (necropsy). No wonder that Mr. B remarked, when his fourth child was taken ill: "I don't know what the matter with the children is, but I am sure that they all have the same thing."

The stable fly (Rosenau and Brues),[11] the bedbug (Howard and Clarke[12]), the rat flea (Richardson[13]) and other insects have been thought to be the agents of conveyance.

We investigated the question of insects and insect-carrying animals at the X House, but failed to find any evidence that insects could have been the source of the infection. The X House and its environs were probably as nearly free from them as any house or locality in the city. There were no fleas, and we cannot find that the stable fly was common in that locality. But aside from these considerations, the theory of the transmission of poliomyelitis by biting insects does not explain the facts of the outbreak at the X House; for one group of children was affected and the other spared; moreover, the children in the affected group developed the disease suddenly, six children (possibly eight) almost together, and the outbreak was begun and ended in two weeks.

We also investigated the sanitary conditions at the X House (garbage disposal, etc.), and the food and water supplies of the different families, without bringing to light any facts indicating the introduction of the infection through those channels. So far as we are aware, there was no single kind of food, or a food derived from a particular source, except perhaps sweetmeats, which was common to the affected families and not to any of the others. The case of the B baby, however, renders the food transmission theory untenable, in one instance at least, for the baby received different food from that of all the other affected children[14] and yet contracted the disease.

The theory of infection through human contact, on the other hand, furnishes the likely interpretation of the facts.

If the analysis of the outbreaks of poliomyelitis in the X House indicates one thing more than another, it is that the primary spreading point of the infection was in the A apartment or connected in some way with the A family, in all probability centering about Harry A. The crux of the problem seemed to be, therefore, to discover how the disease found its way into the A family.

Mr. A was in the habit of going to his office in the city each day by the street cars, but was not aware of contact with any case of poliomyelitis or any sick person. Mrs. A left the X House very little during the period which preceded Harry A's illness, and met, to her knowl-

11. Rosenau, M. J., and Brues, C. T.: Some Experimental Observations on Monkeys Concerning the Transmission of Poliomyelitis Through the Agency of Stomoxys Calcitrans, Tr. XVth Internat. Cong. Hyg. and Demog., 1912, **1,** 616.

12. Howard, C. W., and Clark, P. F.: Experiments on Insect Transmission of the Virus of Poliomyelitis, Jour. Exper. Med., 1912, **16,** 850.

13. Richardson, M. W.: The Rat and Infantile Paralysis; a Theory, Boston Med. and Surg. Jour., 1916, **175,** 397.

14. The baby's food consisted of Walker-Gordon milk and lactose.

edge, no one who had poliomyelitis or any other disease. The colored maid,[15] 19 years old; the laundress, also colored, who did her work outside the A's apartment; P. V.; the boy who drove the pony cart, and P. V.'s friend, were each visited at their homes without bringing to light any association with any case of poliomyelitis there or elsewhere.

The only other person from without who came in contact with the A children during the critical period which preceded Harry A's illness was Mrs. A's father, Mr. W, an elderly man, a resident of New York, and accustomed to travel about extensively. September 6, nine days before Harry A was taken ill, he had come directly from New York, where poliomyelitis was then at its height, to visit his daughter, remained for a day and night in the A's apartment, and while there came in close contact with the children; in Mrs. A's words, "the children climbed all over him." But except for the fact that he came from an infected locality and that the date of his visit preceded the date of his grandson's illness by a comparatively short interval, there seemed to be little reason for supposing him to be the carrier of the disease. We desired to learn whether he had come into contact with poliomyelitis, or had been ill himself prior to his visit to his grandchildren, but were unable to obtain this information. We also sought to test him for poliomyelitis by the inoculation of monkeys with filtrates of his secretions, but without success. We were, therefore, unable to discover the origin of Harry A's illness and of the outbreak in the X House.

We think, however, we have obtained evidence that the disease was transmitted from person to person after it had found entrance to the X House. At least, we have been able to show that all those children developing the disease after Harry A were exposed to Harry A, with the exception of Baby B, and became ill with the disease from three to eight days after the exposure; that Baby B, on the other hand, was in her turn exposed to Bobby B and the other B children, and developed the disease less than nine days afterwards; that all the children exposed to Harry A during his illness developed the disease with the

15. Although we had no evidence to show that the colored maid was the carrier of poliomyelitis, we could not help but regard her with suspicion, because, on the one hand, she lived at home (going to and coming from her work at the A's apartment) in a negro district of the city, and, on the other hand, came into intimate contact, not only with the A children, but with almost all the children who were affected. She left the employ of the A's September 25, the day on which it became known that the B children had poliomyelitis. We visited her home on three different occasions and at the two places of employment which she had obtained after her departure from the A's, but were unable to find that she had been exposed to any case of poliomyelitis prior to Harry A's illness, or that any cases of the disease had developed among those with whom she came in contact after she left the A family, as might have happened had she been a carrier.

exception of Barbara A, Harry A's sister, and perhaps also Ned F and Elizabeth D,[16] and that none of the children not exposed to Harry A (with the exception of Baby B, just mentioned), on the other hand, developed poliomyelitis.

A consideration of the incubation period of all the children calculated on the supposition that the outbreak took origin from Harry A or his environment, also lends support to this view (Table 2). The

TABLE 2.—Giving the Exposure to and Onset of Poliomyelitis in the Children in the X House

September 15, Harry A develops poliomyelitis

	Bobby B	Mary B	Jack C	Charlie B	Dorothy B	Ned F*	Elizabeth D*	Billie C	Baby B
9/16	Exp. A†	.....	.....	.....	.....	Exp. A?			
9/17	Exp. A	.....	.....	Exp. A	.....	Exp. A?			
9/18	Exp. A	Exp. A	.....	Exp. A	Exp. A	Exp. A?			
9/19	Exp. A	Exp. A	.....	Exp. A	Exp. A	Exp. A?			
9/20	Exp A	Exp. A	.....	Exp. A	Exp. A	Exp. A			
9/21	Onset	Exp. A	Exp. A	Exp. A	Exp. A	Exp. A?	Exp. A	Exp. A	Exp. B
9/22	.....	.....	.....	.....	.....	.....	.....	.....	Exp. B
9/23	.....	Onset	.....	.....	.....	.....	.....	.....	Exp. B
9/24	.....	.....	Onset	Onset	Onset	.....	.....	Exp. C	Exp. B
9/25	.....	.....	.....	.....	.....	Onset	Onset	Exp. C	Exp. B
9/26									
9/27									
9/28	.....	.....	.....	.....	.....	.....	.....	Onset	
9/29									
9/30									
10/ 1	.....	.....	.....	.....	.....	.....	.....	.....	Onset

* A definite diagnosis of illness not made.
† Exp. A = exposure to Harry A; Exp. B = exposure to the B children; Exp. C = exposure to Jack C.

shortest incubation period was that of Jack C (exposed to Harry A, September 21, during the drive in the pony cart); it was three days long. The incubation period of his brother, Billy C, was four days, if he acquired the disease from Jack C, seven days if from Harry A during the drive in the pony cart just referred to. His exposure to his brother, Jack C, was particularly close, because the family, not appreciating the nature of Jack C's illness for two days, made no attempt to

16. Ned F and Elizabeth D, it will be remembered, were both taken sick on September 26, four to seven days after their exposure to Harry A, but the data in regard to their illnesses were not sufficient to form a definite judgment.

keep the two boys apart during that time. Bobby B's incubation period was probably five days, though it may have been less. He came in contact with Harry A two to three days before his brother and sisters, and developed the disease two or three days before they did. This rather remarkable correspondence between the time of exposure and of onset made it seem likely that his infection dated from the first day of his exposure to Harry A, which would make the incubation period five days. The incubation periods of Mary B, Dorothy B and Charlie B, calculated from their exposure to Harry A, lie between two and seven days, and seemed fairly definite. (Of course it was possible that Mary, Dorothy and Charlie B contracted the disease from their brother Bobby B, but a consideration of all the facts makes that source of infection less probable.) Baby B's incubation period, calculated from her exposure to her brothers and sister, may have been as short as six days. The contact between her and Bobby B, in the intermission period of the latter's illness, was so intimate (he was repeatedly seen to kiss her) that we have felt inclined to date her infection from that time, which would make the incubation period seven or eight days; but she may have acquired the infection from Bobby B, or the other children later, or from infected material left by them in the apartment (see appendix). In general, it may be said that the estimated incubation periods of the children compare with each other in quite a remarkable way, and that the curve formed by plotting out the dates of known exposure parallels the curve representing the dates of onset as nearly as would obtain if the outbreak had been measles or scarlet fever instead of poliomyelitis. The average duration of the estimated incubation periods is four to five days.[17]

UNUSUAL FEATURES OF OUTBREAK

We wish now to point out several features of the outbreak of poliomyelitis at the X House which are of unusual interest. The first is the remarkable coincidence of the appearance of the disease in all 5 children of one family. Pasteur[18] reported 7 cases in one family, 3 of which were of the paralytic form. The largest number of reported cases of poliomyelitis in any one family during the great New York epidemic of the summer of 1916 was 4.[19] Reece[20] reported the develop-

17. In estimating the above incubation periods we are fully aware of the dangerous ground on which we tread, and wish it to be understood that we regard them only as probable.

18. Pasteur, W.: An Epidemic of Infantile Paralysis Occurring in Children of the Same Family, Tr. Clin. Soc. London, 1897, **30,** 143.

19. Emerson, Haven: Personal communication, 1916.

20. Reece: Proc Roy. Soc. Med. (Epidem. Sec.), 1911-1912, **59.** Rep. Med. Officer, Local Govt. Board, 1912.

ment of 9 cases of poliomyelitis in an ordinary dwelling house, but involving more than one family.

Another interesting feature of the outbreak of poliomyelitis at the X House was the variety of forms in which the disease manifested itself. The case of Bobby B was of the fatal form of *ascending paralysis*. The cases of Harry A, Jack C and Billy C were typical examples of the *nonparalytic* form of the disease. The acute symptoms lasted the full period, five or six days, and their severity was such as to have warranted the assumption that paralysis would follow. The illness of Charlie B and Dorothy B, characterized by violent onset with symptoms suggestive of meningitis, but subsiding within forty-eight hours, are excellent examples of the *abortive* form of the disease. Mary B, on the other hand, represents "masked" poliomyelitis (the "larvierte" form of Müller). This case would never have been recognized except for its association with the others. It is these last two forms which Wickman and others regarded as a special menace to the community.

Another feature of considerable interest is the absence of changes in the spinal fluid in three of the cases, Mary B,[21] Charlie B and Dorothy B. We cannot find in the recent literature a description of any case of poliomyelitis in which the spinal fluid was found to be normal. As a matter of fact, little is known about the spinal fluid in the abortive and "masked" forms of the disease, for the reason that a spinal puncture is almost never made in these cases.

The occurrence of so large a proportion of nonparalytic forms of poliomyelitis among the affected children in the X House is interesting and is probably not so unusual as might first appear, because the milder forms ordinarily escape recognition (Wickman,[1] Leegaard,[22] Müller,[23] Kling, Pettersson and Wernstedt[7] and others. A careful investigation by Wickman of separate outbreaks of poliomyelitis in small isolated Swedish villages for such cases revealed that 35 per cent., 46 per cent. and 56 per cent., respectively, of the total number of cases were nonparalytic. Wickman estimated that 50 per cent. of the cases in epidemics of poliomyelitis were nonparalytic. Leegaard expressed a similar opinion. Edward Müller, who investigated the epidemic of poliomyelitis in Hesse Nassau, Germany, in 1909, came to the conclusion that the abortive forms far exceeded the paralytic, and were especially common among adults. Reece, who studied the "Stokes

21. We should not regard the positive globulin without the presence of alterations in the cellular content as having any special significance.

22. Leegaard, Chr.: Kliniske og Epidemioliske Undersögelser over der akuten Poliomyelit i Norge, Vidensk. Selsk. Skr., Christiania, 1909.

23. Müller, Edward: Die spinale Kinderlahmüng—Eine Klinische und epidemiologische Studie, Berlin, 1910.

River epidemic" of poliomyelitis in England, reported thirty-three abortive cases of poliomyelitis out of a total of thirty-six. Kling, Pettersson and Wernstedt say, "According to our experience the virus carriers and the abortive cases in a family may be four to five times as numerous as the cases showing typical symptoms." And finally, even the statistics of the 1916 New York epidemic show that the nonparalytic cases have been more numerous than those showing paralysis. In the X House, the proportion of nonparalytic cases is over 60 per cent.

Finally, how can we reconcile the facts that in the outbreak at the X House the disease occurred in so severe a form in one case and so mild a form in most of the others? And, what is the significance when the incidence of the disease in a given community is high and the proportion of mild forms relatively great? We can only theorize in answer to these questions. We wish to point out, however, that the severity of the disease in the case of Bobby B may be explained on the ground of excessive physical exertion (it will be remembered that he roller-skated throughout the second and the morning of the third day of his illness). Wickman writes in this connection: "Exercise during the initial stage seems unfavorably to influence the further course of the disease and seems to tend to induce a relapse."

The significance of a high incidence of the disease in a community or a house must be that the infecting material is widespread and easily accessible, so that a large number of persons become infected. The significance of the large proportion of mild cases as observed in all the carefully studied epidemics we would regard as indicating that the larger number of persons are, under ordinary conditions, little susceptible to the disease. If it is true that relatively few are naturally susceptible, it should be found that when the incidence of poliomyelitis is high, the relative number of nonparalytic forms is high; that is, the two vary directly with each other, and the greater the one, the greater also the other.

In conclusion we wish to point out from our experience that a focus of infection in a city or in a house occupied by numerous families or in an institution cannot, from the nature of things, be ideal for the study of the epidemiology of poliomyelitis. The contacts are so numerous that the investigator, attempting to trace the path of the infection, becomes lost in a maze of difficulties. The ideal conditions for such a study are still to be looked for, as Wickman originally pointed out, in a thinly settled community in which contacts occur, but every one of these contacts is an event.

We wish to express our appreciation to Dr. Simon Flexner of the Rockefeller Institute for Medical Research, New York City, and to Dr. G. W. McCoy of the United States Public Health Service, Washington, D. C., for supplying monkeys for some of our experiments.

APPENDIX

We wish to put on record two experiments which were performed in reference to the mode of transmission of the virus of poliomyelitis.

Experimental Attempt to Demonstrate the Virus of Poliomyelitis in Monkey.—Through the health department, a considerable amount of paper and silver money was collected from persons in houses exposed to poliomyelitis. The money was collected in a large, clean, freshly-boiled museum jar which was fitted with a tightly fitting ground glass cover. It was placed directly in the jar by the person from whom it was collected. The money was shaken with a small amount of normal saline solution, the mixture filtered through a Berkefeld filter and the filtrate injected by Dr. G. W. McCoy into a brain ventricle and the peritoneal cavity of a healthy *Macacus rhesus* monkey. Dr. McCoy reports that this monkey did not show any symptoms.

Experimental Attempt to Demonstrate the Virus of Poliomyelitis in Dirt. (in association with Dr. Kenneth D. Blackfan).—Previous to the fumigation of the apartment, and just at the time of the removal (September 25) of the children from the B apartment to the poliomyelitis hospital, the room in which they had remained most of the time of their illnesses was carefully swept. The sweepings, which contained dust, lint, hair, hairpins and a few fruit seeds, were placed in a clean, freshly-boiled museum jar fitted with a tight cover. The material was dry and small in amount.

October 18, the sweepings were covered with a small amount of normal saline solution and left to soak over night in the laboratory. On the following day the mixture was shaken and filtered through a Berkefeld filter. Under ether anesthesia, 2 c.c. of the filtrate were placed in the right lateral ventricle, and 5 c.c. into the peritoneal cavity of a small female *Macacus rhesus* monkey, No. 8. This monkey had been in the laboratory for about four years. She appeared healthy.

The monkey remained well for two days after the injection, at which time she became ill and showed weakness in her left hind leg. On the third day her right hind leg was also weak, and when moving she dragged her hind parts. The illness in every way appeared to be comparable to that observed in Monkey 1. She did not, however, develop any prolapse of the rectum. On the fourth day she appeared very ill, her respirations were rapid—50 per minute.

While under observation at this time she fell, fracturing her skull.

At necropsy the internal organs appeared normal, except for hyperplasia of the lymph node of the intestines, spleen, lungs, mesenteric and bronchial lymph glands. The lumbar and dorsal cord was hyperemic and edematous and there were small hemorrhages in the gray matter of the anterior horns of this region of the cord. The brain and cervical cord appeared normal except for slight congestion and hemorrhage; the latter could be readily referred to fracture of the base of the skull. Microscopic examination of the cord, however, revealed little more than that seen in the gross. There were numerous hemorrhages into the gray matter of the lumbar and dorsal cord. Many of the nerve cells in this region stained deeply, but there was no definite cellular infiltration. Six dorsal root ganglia were examined without revealing anything. Pieces of the lumbar cord of this monkey were taken aseptically and preserved in 50 per cent. glycerin.

Dec. 2, 1916, a thick emulsion in physiologic salt solution of the glycerinated cord of Monkey 8 was injected into Monkey 9.

One cubic centimeter was placed in the right lateral ventricle and 6 c.c. in the peritoneal cavity.

Dec. 12, 1916, a thick emulsion in physiologic salt solution of another part of the glycerinated cord of Monkey 8 was injected into Monkey 6 (Monkey 6 had been used six weeks previously in Experiment 1 (d), but had remained perfectly well).

Two cubic centimeters of the emulsion were placed in the left lateral ventricle and 2 c.c. in the peritoneal cavity.

Both of these monkeys remained well up to the time of writing, Jan. 22, 1917.

THE INFLUENCE OF SPLENECTOMY ON METABOLISM IN ANEMIA*

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Although it has long been known that the removal of the spleen can be effected with impunity, comparatively little data is available regarding the relation of this organ to metabolism. A few experiments made on dogs[1] have led essentially to negative results, while in the four cases[2] in which metabolism studies have been conducted on human subjects, both before and after splenectomy, it was found that more or less definite metabolic changes could be detected after operation.

In the cases studied by Umber, in which splenectomy had been performed on two persons suffering from Banti's disease, this investigator found that after splenectomy it was easier to bring the subjects into nitrogenous equilibrium, a fact which he attributes to the "toxic" action of the spleen in this disease. It was also noted that the output of purins was slightly increased. In one case studied by Minot, a woman suffering from pernicious anemia, it was found that whereas the patient had shown a slight negative nitrogen balance before splenectomy, this changed to a positive balance after operation. This worker also found a slight increase in the percentage of urea nitrogen in the urine after splenectomy.

In a case of congenital hemolytic icterus studied by Goldschmidt and his collaborators, it was observed that a slight positive nitrogen balance before splenectomy was followed by an increased retention after operation; that the output of uric acid showed a decrease of 47 per cent. after operation, and that a large loss of iron through the feces before splenectomy was followed by a decrease of 40 per cent. after operation.

During the past year I have had the opportunity of conducting metabolism experiments before and after removal of the spleen on six patients of this hospital who were operated on for the relief of various types of anemia.[3] In all cases the patients were kept in bed during the

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* From the Chemical Laboratory of the Massachusetts General Hospital.

1. Paton: Jour. Physiol., 1899-1900, **25,** 443. Goldschmidt and Pearce: Jour. Exper. Med., 1915, **22,** 319.

2. Umber: Ztschr. f. klin. Med., 1904, **55,** 289; ibid., München. med. Wchnschr., 1912, **69,** 1478. Minot: Bull. Johns Hopkins Hosp., 1914, **25,** 338. Goldschmidt, Pepper and Pearce: The Archives Int. Med., 1915, **16,** 437.

3. These persons were under the care of Drs. Roger I. Lee, George R. Minot, and Beth Vincent, who have not only allowed me to make use of their patients, but have cooperated in every way towards the successful employment of this material for experimental purposes.

periods of observation, and were under the care of a special nurse trained in metabolism work, who had entire charge of the weighing, cooking and serving of food, the collection of excreta and the drawing of blood. Body temperatures were taken by mouth each day, morning and evening. As no deviation from normal appeared in any case, these observations are not recorded in detail in the tables.

In each case a purin- and creatin-free diet was selected, suitable both qualitatively and quantitatively to the taste of the individual patient. This diet was then used in the presplenectomy as well as in the postsplenectomy periods, the subjects being in each case required to eat all food served them. In looking over the diet lists given below it will be noted that in every case these diets, although of high calorific value, were low in protein (.50 to 65 gm.). This is due to the fact that all of the patients used were possessed of but little appetite, and on this account it seemed best, if they were to be required to eat the entire ration each day, to make this ration of such a nature that it could be consumed with comfort by the subject. In all cases currents were used as a "marker" to separate the feces passed during the experimental periods.

METHODS EMPLOYED

The analytical methods used were as follows:

For Urine: Total nitrogen, urea, ammonia, Folin-Denis methods.[4]

Uric Acid: In Cases 1 and 2 the Folin-Shaffer method was employed; in the remaining cases the determination was made by an as yet unpublished modification of the colorimetric method of Folin and Denis.

Creatinin and Creatin: Folin's micro methods.[5]

Total Sulphur: Benedict's method (as modified by the author[6]).

Ethereal and Inorganic Sulphates: Folin's methods.[7]

Phosphates: By the uranium acetate titration.

For Feces: Total nitrogen by the Kjeldahl methods.

For Blood: Nonprotein nitrogen, Folin-Denis methods;[8] total fat, lecithin and cholesterol, Bloor's methods.[9]

DATA CONCERNING CASES

Case 1.—*Splenectomy for pernicious anemia.*—The first patient studied, Mr. K., 52 years old, was a poorly developed and poorly nourished man weighing only 98 pounds. In this case the disease had probably been in progress for about

4. Folin and Denis: Jour. Biol. Chem., 1916, **26,** 473.
5. Folin: Jour. Biol. Chem., 1914, **17,** 475.
6. Denis: Jour. Biol. Chem., 1910, **8,** 401.
7. Folin: Jour. Biol. Chem., 1905, **1,** 131.
8. Folin and Denis: Jour. Biol. Chem., 1916, **26,** 491.
9. Bloor: Jour. Biol. Chem., 1915, **23,** 317; ibid., 1916, **24,** 227 and 450.

one year. The data concerning the past history, physical examination, etc., will not be given here as they offered nothing of interest in connection with this work.

Blood examination made on the first day of observation during the presplenectomy period showed:

Red cells	1,200,000
White cells	3,000
Hemoglobin (Sahli)	35 per cent.

The patient was splenectomized, March 1, by Dr. Beth Vincent. He made a rapid and uneventful recovery, and twenty-six days after the operation a second period of observation was begun.

Blood examination made of the first day of this period showed:

Red cells	2,500,000
White cells	7,100
Hemoglobin	80 per cent.

The food served was the same each day and consisted of the following:

	Gm. or c.c.
Oranges (selected to weigh 150 gm.)	4
Eggs (selected to weigh 50 gm.)	3
Oatmeal	37
Bread	120
Sugar	80
Potato	150
Peas (canned)	100
Butter	80
Cream (40 per cent. fat)	250
Milk (3.5 per cent. fat)	350

Mr. K. consumed the above diet for six days before splenectomy. The excreta passed during the first two days of this period were discarded, only that secured during the last five days being analyzed. Twenty-five days after splenectomy another experimental period of six days was begun, and here, as before, only the excreta passed during the last five days of the period were analyzed.

Case 2.—*Splenectomy for pernicious anemia.*—The second patient, Mr. B., was 28 years old and weighed 120 pounds. His illness had been in progress about thirteen months. His family history, past history, and the results of the physical examination present nothing of interest in connection with the work described in this paper, and will therefore be omitted.

Blood examination made on the first day of the presplenectomy period showed:

Red cells	824,000
White cells	2,000
Hemoglobin	38 per cent.

Splenectomy was performed, May 15, by Dr. Beth Vincent. Recovery was rapid and May 28, thirteen days after operation, a second series of metabolism observations was begun. At this time an examination of the blood gave the following results:

Red cells	2,100,000
White cells	8,000
Hemoglobin	60 per cent.

The daily ration served to this patient during both the presplenectomy and postsplenectomy periods was as follows:

	Gm. or c.c.
Grape fruit	100
Orange	150
Cream of wheat	25
Bread	150
Crackers	25
Butter	60
Eggs (selected to weigh 50 gm. gross)	3
Cream (40 per cent. fat)	250
Whole milk (3.5 per cent. fat)	250
Sugar	80
Potato	100
Onions	100
Tomato	100
Lettuce	40

Mr. B. consumed the above diet for seven days before splenectomy, and for a like period after the operation. In both cases the excreta collected on the first two days of the experimental period were discarded, only the excreta passed on the last five days being analyzed.

CASE 3.—*Splenectomy for Banti's disease.*—The third patient, Miss C., was 17 years old and weighed 86 pounds.

The patient knew nothing of her parents, but stated that she had always been yellow since an attack of jaundice in early childhood, the exact date of which she was unable to recall. At the time of entering the hospital her skin was markedly pigmented, the sclera being also slightly icteroid.

Physical examination showed nothing of interest except a mass on the right side of the abdomen which was felt 6½ cm. from the midsternal line, and which protruded from under the right costal border. This mass was considered by the medical and surgical consultants to be an enlarged spleen.

Blood examination made on the first day of the presplenectomy period showed:

Red Cells	2,292,000
White cells	8,100
Hemoglobin	55 per cent.

The spleen, which weighed 611 gm., was removed, May 31, by Dr. Beth Vincent. The patient made an uneventful recovery and on June 14 a second series of observations was begun. At this time blood examination gave the following results:

Red cells	4,200,000
White cells	126,000
Hemoglobin	110 per cent.

The changes produced by splenectomy on the physical characteristics of the urine in this case were very striking. Before operation the urine was invariably of the deep mahogany brown color characteristic of hemolytic jaundice. In the urine passed as early as twenty-five hours after operation this color had markedly diminished, and in that passed three days after splenectomy it had entirely disappeared.

The daily ration taken by Patient 3 was as follows:

	Gm. or c.c.
Milk (3.5 per cent. fat)	250
Cream (40 per cent. fat)	180
Butter	60
Egg (selected to weigh 50 gm. gross)	1
Sugar	40

	Gm. or c.c.
Bread	225
Orange	100
Potato	100
Carrots	100
Asparagus	100
Lettuce	40
Turnips	100
Cocoa (powder)	8
Oatmeal	25

CASE 4.—*Splenectomy for hereditary jaundice.*—The fourth patient, Mr. W., was 29 years old and weighed 118 pounds. Aside from chronic jaundice, from which he had suffered since early childhood, the patient had always been well until about six months before entrance into the hospital. Physical examination showed a well developed but poorly nourished young man, with skin and sclera both distinctly yellow. The spleen was barely palpable.

Blood examination made on the first day of the presplenectomy observation period gave the following results:

Red cells	3,882,000
White cells	15,550
Hemoglobin (Sahli)	101 per cent.

Splenectomy was performed, July 1, by Dr. Beth Vincent. Recovery was rapid, and ten days later a second series of observations was made.

Blood examination made at this time showed:

Red cells	4,568,000
White cells	20,400
Hemoglobin (Sahli)	106 per cent.

The daily ration taken by this patient consisted of the following:

	Gm. or c.c.
Grape fruit	150
Pineapple	100
Cornmeal	25
Bread	150
Potato	250
Butter	40
Milk (3.5 per cent. fat)	100
Cream (40 per cent. fat)	360
Eggs (selected to weigh 50 gm. gross)	3
Gelatin	50
Cocoa	8
Sugar	80
Lettuce	65
Asparagus	100

CASE 5.—*Splenectomy for "Atypical splenic anemia."*—The fifth patient, Mrs. L., 38 years old, and weighing 139 pounds, had been suffering for about one year with an abdominal tumor which had increased in size steadily and progressively. This tumor was believed by the surgical and medical consultants to be an enlarged spleen, and splenectomy was advised.

Blood examination made on the first day of the presplenectomy period showed:

Red cells	4,620,000
White cells	17,000
Hemoglobin (Sahli)	85 per cent.

November 10, splenectomy was performed by Dr. Beth Vincent. The following description of the spleen is taken from the report of the pathologist (Dr. Hartwell).

"A large thick spleen weighing 140 gm. Microscopic examination gives the appearance of a richly cellular tumor with a reactionary fibrosis. The cells are similar to those of the bone marrow, namely, various forms of myelocytes, nucleated red, and large multinucleated cells suggesting megakaryocytes. The histologic structure is similar to that seen in myelogenous leukemia."

Recovery after operation was rapid, and as the patient was anxious to return home as promptly as possible, a second period of observation was begun seven days after splenectomy.

The daily ration served this patient was as follows:

	Gm. or c.c.
Oranges (selected to weigh 150 gm. gross)	2
Grape fruit (selected to weigh 200 gm. gross)	1
Eggs (selected to weigh 50 gm. gross)	2
Shredded wheat	25
Oatmeal	37
Bread	125
Potato	150
Lettuce	25
Tomato	100
Butter	80
Milk (3.5 per cent.fat)	300
Cream (40 per cent. fat)	200
Sugar	50

CASE 6.—*Splenectomy for Banti's Disease.*—The sixth patient, Mr. C., 46 years old, weighed 139 pounds. For the previous year the patient had been suffering from pain in his back, legs and feet, and for the previous six months his abdomen had been increasing in size, and he had been troubled with a feeling of weakness which had made it necessary for him to abandon his work as an operative in a shoe factory.

Blood examination made on the first day of the experimental period gave the following results:

Red cells	2,688,000
White cells	4,200
Hemoglobin	54 per cent.

Splenectomy was performed, November 28, by Dr. Beth Vincent, the spleen weighing 1,640 gm. Recovery was rapid, and seven days later a second period of observation was commenced.

The daily ration served to this patient was as follows:

	Gm. or c.c.
Banana	150
Orange	100
Eggs (selected to weigh 50 gm gross)	3
Bread	125
Potato	75
Peas (canned)	50
Corn (canned)	50
Butter	60
Milk (3.5 per cent. fat)	500
Cream (40 per cent. fat)	250
Sugar	50

TABLE 1.—Case 1 (Pernicious Anemia)

Date	Wt. Kg.	Vol. of Urine, C.c.	Total Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinin, Gm.	Creatin, Gm.	Uric Acid, Gm.	Total Phosphates as P_2O_5, Gm.	Feces
Before Splenectomy									
2/21–22	44.5	1,222	5.98	0.36	0.71	0	0.21	1.22	Mixed feces for 4 days, dry wt., 285 gm.; nitrogen, 10.62 gm.
2/22–23	....	980	4.90	0.29	0.72	0	0.18	1.03	
2/23–24	....	940	5.68	0.35	0.70	0	0.18	0.80	
2/24–25	....	940	4.48	0.30	0.72	0	0.18	0.72	
			20.99	1.30	2.84	0	0.75	3.77	
After Splenectomy									
3/28–29	45.8	800	6.80	0.35	0.68	0	0.26	1.24	Mixed feces for 4 days, dry wt., 99.8 gm.; nitrogen, 5.12 gm.
3/29–30	....	820	6.18	0.38	0.73	0	0.28	1.46	
3/30–31	....	920	6.49	0.36	0.68	0	0.24	1.75	
3/31–4/1	....	960	6.69	0.38	0.72	0	0.26	2.09	
			26.16	1.47	2.81	0	1.04	6.44	

TABLE 2.—Case 2 (Pernicious Anemia)

Date	Wt. Kg.	Vol. of Urine, C.c.	Total Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinin, Gm.	Creatin, Gm.	Uric Acid, Gm.	Total Phosphates as P_2O_5, Gm.	Feces
Before Splenectomy									
5/ 8– 9	54.5	880	7.70	0.27	1.00	0	0.59	0.97	Mixed feces for 5 days, dry wt., 81.0 gm.; nitrogen, 4.07 gm.
5/ 9–10	....	1,240	8.30	0.31	0.99	0	0.63	1.58	
5/10–11	....	1,250	8.35	0.38	1.08	0	0.60	1.21	
5/11–12	....	1,020	6.12	0.29	1.06	0	0.57	1.08	
5/12–13	....	1,000	5.75	0.28	1.05	0	0.55	1.09	
			36.22	1.53	5.18	0	2.94	5.93	
After Splenectomy									
5/31–6/1	52.2	1,000	5.55	0.42	1.05	0	0.47	1.09	Mixed feces for 5 days, dry wt., 135 gm.; nitrogen, 5.55 gm.
6/1–2	....	1,400	6.79	0.45	1.08	0	0.54	1.41	
6/2–3	....	1,460	7.44	0.47	1.08	0	0.54	1.23	
6/3–4	....	1,220	5.61	0.40	1.00	0	0.54	1.42	
6/4–5	....	1,360	6.60	0.46	0.99	0	0.53	0.95	
			31.99	2.20	5.20	0	2.62	6.10	

TABLE 3.—Case 3 (Banti's Disease)

Date	Wt. Kg	Vol. of Urine, C.c.	Total Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinin, Gm.	Creatin, Gm.	Uric Acid, Gm.	Total Phosphates as P_2O_5, Gm.	Feces
Before Splenectomy									
5/26–27	39.0	700	4.65	0.44	0.58	0.19	0.60	0.83	Dry weight of mixed stools for five days, 108 gm.; nitrogen, 5.77 gm.
5/27–28	....	700	4.06	0.40	0.56	0.09	0.49	0.61	
5/28–29	....	560	3.93	0.37	0.59	0.14	0.47	0.60	
5/29–30	....	1,020	4.13	0.40	0.58	0.10	0.50	0.73	
5/30–31	....	680	3.30	0.37	0.58	0.05	0.50	0.77	
			20.07	1.98	2.89	0.57	2.46	3.54	
After Splenectomy									
6/16–17	33.6	980	5.09	0.33	0.50	0.07	0.38	0.51	Dry weight of mixed stools for five days, 90 gm.; nitrogen, 5.10 gm.
6/17–18	....	550	4.20	0.42	0.46	0.17	0.36	0.75	
6/18–19	....	1,020	5.35	0.37	0.48	0.11	0.39	0.95	
6/19–20	....	530	4.00	0.39	0.47	0.08	0.36	0.85	
6/20–21	....	700	3.90	0.39	0.48	0.09	0.31	0.82	
			22.54	1.90	2.39	0.52	1.80	3.00	

TABLE 4.—Case 4 (Family Jaundice)

Date	Wt. Kg.	Vol. of Urine, C.c.	Total Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinin, Gm.	Creatin, Gm.	Uric Acid, Gm.	Total Phosphates as P_2O_5, Gm.	Feces
Before Splenectomy									
6/24–25	53.6	840	10.90	0.40	1.20	0.14	0.41	1.24	Total dry weight of mixed feces for five days, 80.0 gm.; nitrogen, 4.35 gm.
6/25–26	....	1,520	9.74	0.47	1.26	0.38	0.48	1.06	
6/26–27	....	2,200	7.55	0.57	1.27	0.05	0.45	1.22	
6/27–28	....	1,400	9.99	0.52	1.28	0.30	0.49	1.96	
6/28–29	....	1,200	10.89	0.39	1.30	0.00	0.40	1.40	
			49.07	2.35	6.31	0.87	2.23	6.88	
After Splenectomy									
7/11–12	50.0	1,160	10.33	0.24	1.22	0.06	0.50	1.92	Total dry weight of mixed feces for five days, 79.0 gm.; nitrogen, 3.96 gm.
7/12–13	....	1,140	9.77	0.29	1.21	0.21	0.44	1.86	
7/13–14	....	770	9.33	0.28	1.19	0.00	0.38	2.02	
7/14–15	....	850	9.37	0.21	1.15	0.00	0.38	2.37	
7/15–16	....	1,140	11.10	0.34	1.17	0.00	0.45	1.48	
			49.90	1.33	5.94	0.27	2.15	9.65	

TABLE 5.—Case 5 ("Atypical Splenic Anemia")

Date	Wt. Kg.	Vol. of Urine, C.c.	Total Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinin, Gm.	Creatin, Gm.	Uric Acid, Gm.	Total Phosphates as P_2O_5, Gm.	Feces
Before Splenectomy									
11/1–2	6.31	380	4.42	0.35	0.84	0.13	0.42	0.97	Dry weight of mixed feces for four days, 125 gm.; nitrogen, 6.76 gm.
11/2–3	....	470	4.80	0.35	0.78	0.36	0.42	0.88	
11/3–4	....	460	3.89	0.38	0.79	0.45	0.44	0.80	
11/4–5	....	1,160	4.46	0.46	0.94	0.12	0.42	0.81	
			17.57	1.54	3.35	1.06	1.70	3.46	
After Splenectomy									
11/19–20	....	460	5.80	0.41	0.85	0.10	0.56	0.80	Dry weight of mixed feces for four days, 109 gm.; nitrogen, 5.28 gm.
11/20–21	....	510	5.75	0.50	0.86	0.11	0.53	0.96	
11/21–22	....	560	5.95	0.54	0.91	0.33	0.56	1.00	
11/22–23	....	850	5.60	0.45	0.84	0.24	0.60	1.07	
			23.10	1.90	3.46	0.78	2.25	3.83	

TABLE 6.—Case 6 (Banti's Disease)

Date	Wt. Kg.	Vol. of Urine, C.c.	Total Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinin, Gm.	Creatin, Gm.	Uric Acid, Gm.	Total Phosphates as P_2O_5, Gm.	Feces
Before Splenectomy									
11/21–22	63.1	520	8.05	0.57	1.10	0	0.58	1.10	Dry weight of mixed feces for four days, 62 gm.; nitrogen, 2.9 gm.
11/22–23	....	820	6.76	0.46	0.97	0	0.55	1.14	
11/23–24	....	780	6.12	0.52	0.91	0	0.59	0.94	
11/24–25	....	870	6.44	0.66	0.98	0	0.53	0.72	
			27.37	2.21	3.96	0	2.25	3.90	
After Splenectomy									
12/6– 7	61.0	1,390	7.39	0.35	0.98	0	0.61	1.39	Dry weight of mixed feces for four days, 69 gm.; nitrogen, 3.2 gm.
12/7– 8	....	1,000	7.15	0.58	0.86	0	0.51	1.15	
12/8– 9	....	1,800	7.92	0.47	0.99	0	0.55	1.09	
12/9–10	....	1,560	7.61	0.42	0.94	0	0.57	1.12	
			30.07	2.02	3.77	0	2.24	4.75	

INFLUENCE OF SPLENECTOMY ON NITROGENOUS METABOLISM

1. Total Nitrogen of Urine and Feces.—No attempt was made in any case to obtain nitrogen balances, as it was felt that the time during which the patients could be detained for experimental purposes (about ten days) was insufficient to give reliable results from such work.

In general, no characteristic or constant effect which could be directly attributed to the removal of the spleen was found in the study of nitrogen excretion. It is not without interest to note, however, that in four of the six cases studied, the urinary nitrogen was distinctly increased during the postsplenectomy period, and that this increase in urinary nitrogen was accompanied by a corresponding decrease in the fecal nitrogen.

2. Ammonia. — In four cases no appreciable difference in the ammonia excretion was found in the two periods; in Case 2 (pernicious anemia) the ammonia in the second period is considerably higher than in the first (2.20 as against 1.52 gm.), while in Case 4 (family jaundice) the opposite result was obtained.

3. Creatinin and Creatin.—No change in the creatinin excretions was noted after operation in any case.

Creatin was absent from the urine in Cases 1, 2 and 6; it was present in the urines in Cases 3, 4 and 5, both before and after operation.

4. Uric Acid.—In three cases (2, 4 and 6) the uric acid figures obtained before splenectomy were practically the same as those found after operation. In two cases (1 and 5) there was a marked increase in the uric acid output after splenectomy, while in one case (3) the quantity of uric acid excreted in the second period was much lower than that found in the first.

5. Phosphates.—In five cases there was an increase in phosphate excretion in the postoperative period, which, while small in some cases (2), was very considerable in others (1 and 4), while in one case (3) a slight decrease was found. No parallelism, however, was apparent between this increased phosphate excretion and the output of total nitrogen or of uric acid.

INFLUENCE OF SPLENECTOMY ON THE SULPHUR METABOLISM

The sulphur partition was studied in two cases of pernicious anemia (Cases 1 and 2), one of Banti's disease (Case 3), and one of family jaundice (Case 4).

In all four the results obtained are similar. The partition of sulphur between inorganic sulphates, ethereal sulphates and neutral sulphur is essentially normal; no change occurred either in the distribution or in the absolute amounts of the fractions after splenectomy,

except in Case 1, in which it will be noted that the ethereal sulphates are reduced in amount in the post splenectomy period, a phenomenon which is explained by the fact that whereas during the preoperative period the patient was constipated, so that the bowels moved only by means of enemata (given every forty-eight hours), in the postoperative period two to three spontaneous movements occurred each day.

TABLE 7.—Case 1 (Pernicious Anemia) Sulphur Metabolism

Date	Total Sulphur as SO_3, Gm.	Inorganic Sulphates as SO_3, Gm.	Ethereal Sulphates as SO_3, Gm.	Neutral Sulphur as SO_2, Gm.	Per Cent. of Total Sulphur		
					Inorganic Sulphates	Ethereal Sulphates	Neutral Sulphur
Before Splenectomy							
2/21–22	1.09	0.70	0.14	0.24	64.51	12.95	22.54
2/22–23	1.26	0.91	0.17	0.18	71.94	13.19	14.87
2/23–24	1.14	0.75	0.20	0.19	65.79	17.14	17.06
2/24–25	1.02	0.70	0.10	0.21	69.25	9.41	21.34
After Splenectomy							
3/28–29	1.30	1.04	0.02	0.24	79.62	1.84	18.42
3/29–30	1.25	0.90	0.09	0.26	72.03	6.92	21.05
3/30–31	1.14	0.92	0.05	0.16	80.19	4.46	15.05
3/31–4/1	1.05	0.77	0.09	0.23	73.18	8.52	18.30

TABLE 8.—Case 2 (Pernicious Anemia) Sulphur Metabolism

Date	Total Sulphur as SO_3, Gm.	Inorganic Sulphates as SO_3, Gm.	Ethereal Sulphates as SO_3, Gm.	Neutral Sulphur as SO_2, Gm.	Per Cent. of Total Sulphur		
					Inorganic Sulphates	Ethereal Sulphates	Neutral Sulphur
Before Splenectomy							
5/ 8– 9	1.53	1.17	0.11	0.25	77.17	7.11	15.72
5/ 9–10	1,78	1.31	0.07	0.40	77.21	3.71	19.08
5/10–11	1.42	1.07	0.12	0.23	75.35	8.45	16.20
5/11–12	1.17	0.86	0.08	0.23	73.56	6.59	19.81
5/12–13	1.23	0.73	0.14	0.36	70.61	11.38	18.01
After Splenectomy							
5/31–6/1	1.40	0.89	0.10	0.40	64.00	7.43	28.57
6/1–2	1.21	0.84	0.12	0.24	69.44	9.99	20.57
6/2–3	1.53	1.03	0.14	0.36	67.55	7.54	24.91
6/3–4	0.97	0.73	0.09	0.15	75.16	8.75	18.09
6/4–5	1.36	1.00	0.10	0.25	73.23	7.46	19.31

TABLE 9.—Case 3 (Banti's Disease) Sulphur Metabolism

Date	Total Sulphur as SO_3, Gm.	Inorganic Sulphates as SO_3, Gm.	Ethereal Sulphates as SO_3, Gm.	Neutral Sulphur as SO_2, Gm.	Per Cent. of Total Sulphur		
					Inorganic Sulphates	Ethereal Sulphates	Neutral Sulphur
Before Splenectomy							
5/26–27	1.29	0.87	0.16	0.25	77.27	12.39	15.34
5/27–28	1.05	0.73	0.12	0.20	81.11	13.40	18.84
5/28–29	1.14	0.75	1.10	0.20	65.90	8.93	18.12
5/29–30	0.98	0.61	0.15	0.21	62.78	15.71	21.51
5/30–31	0.69	0.43	0.10	0.14	64.35	15.02	20.65
After Splenectomy							
6/16–17	1.16	0.79	0.13	0.23	68.51	11.40	20.09
6/17–18	1.24	0.70	0.27	0.26	56.43	22.46	21.08
6/18–19	1.03	0.65	0.15	0.22	63.01	14.65	22.34
6/19–20	1.11	0.68	0.15	0.28	60.80	13.75	25.39
6/20–21	0.85	0.54	0.13	0.16	61.19	15.93	22.88

TABLE 10.—Case 4 (Family Jaundice) Sulphur Metabolism

Date	Total Sulphur as SO_3, Gm.	Inorganic Sulphates as SO_3, Gm.	Ethereal Sulphates as SO_3, Gm.	Neutral Sulphur as SO_2, Gm.	Per Cent. of Total Sulphur		
					Inorganic Sulphates	Ethereal Sulphates	Neutral Sulphur
Before Splenectomy							
6/24–25	1.93	1.44	0.10	0.39	74.01	5.08	20.91
6/25–26	1.78	1.24	0.18	0.35	69.62	10.58	19.80
6/26–27	1.53	1.07	0.14	0.31	70.11	9.18	20.61
6/27–28	2.22	1.58	0.24	0.39	71.23	10.92	17.85
6/28–29	1.84	1.30	0.18	0.36	70.92	9.67	19.41
After Splenectomy							
7/11–12	1.85	1.44	0.19	0.22	77.09	10.71	12.20
7/12–13	1.82	1.39	0.11	0.30	75.99	6.49	17.52
7/13–14	1.64	1.31	0.08	0.25	79.78	4.56	15.56
7/14–15	1.56	1.04	0.24	0.28	67.02	15.96	17.02
7/15–16	1.77	1.23	0.13	0.33	72.67	8.07	19.26

INFLUENCE OF SPLENECTOMY ON THE BLOOD

In view of the great importance which has recently been assigned to the spleen in connection with fat and lipoid metabolism by King, by Eppinger and by Medak,[10] it has seemed desirable to make analyses

10. King, J. H.: Studies in the Pathology of the Spleen, The Archives Int. Med., 1914, **14,** 145. Eppinger: Medak: Biochem. Ztschr., 1914, **59,** 419.

of the blood lipoids of these patients both before and after operation. The microchemical methods recently introduced by Bloor make it possible to determine the more important lipoids (fats, lecithin and cholesterol) in the comparatively small amounts of blood which it was considered permissible to take from these patients. Determinations of nonprotein nitrogen have also been made, but on account of lack of material it was necessary to omit determinations of the other blood constituents, such as uric acid, creatinin, etc.

The results presented in Table 11 show that in the five cases in which blood analyses were made, practically no change in the nonprotein nitrogen or total fatty acids of the blood was observed, except

TABLE 11.—CHEMICAL EXAMINATION OF BLOOD BEFORE AND AFTER SPLENECTOMY *

		Nonprotein Nitrogen, Mg. per 100 Gm. Blood	Corpuscles, per Cent.	Total Fatty Acids, per Cent.		Lecithin, per Cent.		Cholesterol, per Cent.	
				Whole Blood	Plasma	Whole Blood	Plasma	Whole Blood	Plasma
Case 1	Before.....	35	22	0.32	0.27	0.25	0.16	0.13	0.11
	After.....	34	26	0.31	0.24	0.28	0.16	0.21	0.20
Case 2	Before.....	23	14	0.35	0.35	0.16	0.16	0.15	0.15
	After.....	25	17	0.38	0.30	0.21	0.17	0.13	0.13
Case 4	Before.....	31	..	0.24	....	0.15	....	0.15	
	After.....	30	31	0.34	0.30	0.18	0.15	0.18	0.16
Case 5	Before.....	..	37	0.46	0.49	0.24	0.20	0.16	0.14
	After.....	..	34	0.47	0.44	0.32	0.22	0.19	0.19
Case 6	Before.....	..	29	0.68	0.55	0.28	0.16	0.16	0.14
	After.....	..	30	0.62	0.54	0.31	0.22	0.17	0.15

* I am indebted to Dr. W. R. Bloor for the determinations of the blood lipoids.

in Case 4, in which the fatty acid figure obtained after splenectomy was considerably higher than that found in the blood sample taken before operation. Lecithin was slightly increased in the whole blood, and also showed somewhat higher values in the plasma in Cases 5 and 6. Cholesterol was increased in both whole blood and plasma except in Case 2, in which a slight decrease was found. On the whole, the results obtained do not confirm the results of Eppinger and of King regarding the increased content of fat after splenectomy. They are, however, in accordance with the statements of these authors concerning the increased blood cholesterol found after splenectomy.

SUMMARY

Metabolism studies have been conducted before and after operation in six cases of anemia in which splenectomy was performed. These included two cases of pernicious anemia, two of Banti's disease, one of family jaundice and one of "atypical splenic anemia."

It was found that while, in some of the cases examined, changes in the excretion of certain bodies occurred, these changes were not constant; thus in two cases the uric acid output was much increased after operation, in one it was reduced, while in three no change was noted.

In a series of observations on the phosphate excretion it was found that while in five cases the output of phosphates by the kidney was increased after operation, in one (Case 3) it was decreased.

It is of interest to note that there is no relation between these changes in uric acid and phosphate excretion and the increase in leukocytes noted in the blood counts made during the postoperative period. Thus in Case 3, 8,100 white blood cells were present during the first period and 126,000 during the second, whereas there is a decrease in the excretion of phosphates and uric acid. In Case 1, however, the white blood cells increased only from 3,000 to 7,100, while the uric acid and phosphate excretion was almost doubled.

A study of the sulphur excretion showed no changes, either relative or absolute, which could in any way be attributed to the removal of the spleen.

Blood analyses did not confirm the findings of King and Eppinger regarding the increased content of fat in the blood after splenectomy; cholesterol was found to be more or less increased in every case. I have noted in several cases, however, that in anemia the low blood cholesterol figures so commonly found in this disease almost invariably increase noticeably when the blood picture is improved, whether this be accomplished by transfusion or by spontaneous remission.

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THE ELECTROCARDIOGRAM; ITS RELATION TO CARDIODYNAMIC EVENTS*

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I. INTRODUCTION

A clearer conception of the temporal relation that each variation of the electrocardiogram bears to systole and diastole of the auricles and ventricles is of twofold importance. It is essential, if the electrocardiogram is to be utilized, directly or indirectly, as a diagnostic criterion of the functional capacity of the heart. It is indispensable in explaining the ultimate cause of the electrocardiogram variations, for obviously no dynamic process can be held responsible for any electrical variation with which it is not isochronous.

In discussing the time relations it is important to be oriented as to the precise events that merit comparison. It is quite generally recognized that the electrical variations recorded in the electrocardiogram by the three customary leads do not occur in an invariable relation to each other or to a definite phase of the cardiac cycle.

Einthoven,[1] in 1908, first directed attention to the fact that *peaks* bearing the same letter occur in different phases of the cardiac cycle. Kahn[2] found that if the summit of P is used as a standard, then peak RI precedes peak RII and this in turn comes earlier than peak RIII. In transcribed curves published by Fahr[3] and Einthoven, Fahr and Waart[4] peaks RII and RIII are synchronous, but later than peak RI. These differences are not only relative to other waves, but real, as shown by simultaneous leads taken during identical heart cycles. In carefully measured curves Williams[5] found the relations variable and not to be predicted. In three cases RI was delayed (0.006 second); in two cases RI and RII were in phase and preceded by RIII; in one case all peaks were in phase.

The phase difference of the summit of the P wave is even greater. In one case Williams[5] found the summit of PI to be 0.02 second later than the summits of PII and PIII. Differences as great as 0.04 second are shown in the curves published by Fahr[3] and Einthoven, Fahr and Waart.[4] Uniformly the summit of PI seems to be delayed.

The initial rise of the P and R waves is quite variable in different leads. In the case of the P wave this is due in part to the difficulty of determining exactly the initial rise. In the case of the R wave, the presence of a Q depression in one lead and its absence in another often complicate the question. Hoffmann[6] concluded that the rises of RI and RII occur simultaneously, but

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1. Einthoven: Arch. f. d. ges. Physiol., 1908, **122,** 588.
2. Kahn: Arch. f. d. ges. Physiol., 1909, **129,** 291; Ergebn. d. Physiol., 1914, **14,** 69.
3. Fahr: Heart, 1912-1913, **4,** 147.
4. Einthoven, Fahr and Waart: Arch. f. d. ges. Physiol., 1913, **150,** 275.
5. Williams: Am. Jour. Physiol., 1914, **35,** 295.
6. Hoffmann: Zentralbl. f. Herz. u. Gefässkrankh., 1912, **4,** 187.

that the rise of RIII is delayed. According to Kahn,[2] the beginnings of QI, QII and QIII are progressively delayed when compared with the summit of P. According to one of the plotted curves of Fahr,[8] the rise of RII and RIII are synchronous, while the rise of RI is delayed; in another curve the initial deflection of R coincides in Leads I and III but is delayed in Lead II. In simultaneous leads published by Williams, RI and RII begin synchronously, but the rise of RIII is delayed fully 0.01 second.

The necessity of selecting a *standard lead* for all time comparisons with dynamic events is evident. For this purpose Lead II has been almost universally used, not only because the waves are larger and more certain in the direction of the deflections, but also because their relation to the electrical negativity of different regions of the heart has been experimentally established (see accompanying figure). By comparing with an auricular myogram, first the electrical variations of Lead II and then the time of initial negativity at the sinus node, Eyster and Meek[7] found that the rise of PII begins approximately 0.01 second after initial negativity of the sinus node appears. By simultaneously recording the electrocardiogram by Lead II and the initial negativity of the exposed heart, Lewis, Meakins and White[8] were able to confirm this relation. They further showed that within 0.03 second the wave of negativity had reached the right auricular appendage and within 0.045 second the ear of the left auricle. It is interesting to note that this corresponds practically to the summit of PII (see figure).

The earliest evidence of negativity in the ventricle, according to Lewis and Rothschild,[9] occurs 0.01 to 0.015 second before the upstroke of RII, or about 0.005 second before the QII depression when present. The "central region" of the right ventricle is negative, almost simultaneous with the onset of RII. According to Erfmann,[10] the entire ventricular surface then becomes negative within a few thousandths of a second, but the more detailed investigations of Lewis and Rothschild[9] show that at least 0.02 to 0.03 second is required before the negative wave has spread over the entire ventricular surface. This point coincides approximately with the summit of RII.

II. RELATION OF THE ELECTRICAL VARIATIONS TO AURICULAR SYSTOLE

Inasmuch as the P-R interval approximately corresponds to the period assigned to auricular systole by Marey,[11] Einthoven and de Lint[12] at first attributed both the P elevation and Q depression to

7. Eyster and Meek: THE ARCHIVES INT. MED., 1913, **11,** 233.
8. Lewis, Meakins and White: Phil. Tr. Roy. Soc. London, 1914-1915, B, **205,** 381.
9. Lewis and Rothschild: Phil. Tr. Roy. Soc. London, 1914-1915, B, **206,** 219.
10. Erfmann: Ztschr. f. Biol., 1913, **61,** 155.
11. Marey: La circulation du sang, 1881, p. 96.
12. Einthoven and de Lint: Arch. f. d. ges Physiol., 1900, **80,** 139.

auricular systole. Later, on finding that the Q depression always precedes R rather than follows P when the auricular contraction does not occupy a presystolic position, Einthoven[13] concluded that the Q depression is due to ventricular systole.

Many attempts have since been made to establish more precisely the relation of the P wave to auricular systole. We may pass at once to a review of the experimental work, since the efforts to establish the relation to auricular systole in man by the aid of the venous pulse and apex cardiograms have been and must continue to be futile. Neither gives any precise information regarding the onset of auricular contraction.

Relation to the Onset of Auricular Contraction.—In experimental animals the electrocardiogram waves have frequently been related to the onset of the mechanical contraction curve recorded by attaching a light lever, through a string, with an auricular appendage. The comparison of the electrical variations with such a "suspension curve" simultaneously recorded, indicates that the mechanical contraction not only occurs later than the rise of the P wave, but that it does not even begin until the P wave has been practically completed. As examples, we may consider the results of Kahn,[14] showing a delay of 0.04 to 0.05 second, and those of Eyster and Meek,[7] showing a delay of 0.07 second in the mechanical response.

Such results readily lead to the conclusion that the P wave is not associated with auricular contraction, but rather with the conduction of impulses across the auricles. Before such an assumption may be made it is clearly necessary to satisfy ourselves that the methods employed to determine the onset of systole equal in their sensitiveness and accuracy the method used to detect variations in electrical potential. In a recent series of papers[15] dealing with the physiology of the mammalian auricle, reasons were given to show why the "suspension curve" of the auricle cannot be trusted to indicate even the onset of auricular systole correctly. Furthermore, an accurate myogram recorded from two approximating points on the auricular surface also does not show the onset of mechanical contraction. The reasons for this seem to be clear: Not all portions of the auricular muscle are excited simultaneously, but each fractionate portion of muscle is successively excited as the impulse spreads radially from the sinus node to the more distant fractions. A myogram recorded from the anterior auricular surface or appendage, therefore, does not indicate the earliest movement of the auricular muscle near the sinus region. Experiments[15] have shown

13. Einthoven: Arch. internat. de physiol., 1906, **4,** 132.
14. Kahn: Arch. f. d. ges Physiol., 1910, **132,** 209.
15. Wiggers: Am. Jour. Physiol., 1916, **40,** 218; ibid., **42,** 133 and 141.

that the intra-auricular pressure rises approximately 0.02 second earlier than the deflection of the auricular myogram. The intra-auricular pressure curve evidently gives a very much more accurate indication of the onset of mechanical systole of the auricle.

Using this as a standard of comparison, Kahn[16] obtained very variable relations. Lewis[17] publishes a diagram, apparently based on uncited experiments, which places the initial rise of intra-auricular pressure 0.04 second after the rise of PII. This work was done before accurate forms of recording manometers were available. The first comprehensive study of this question was carried out by Garten and Weber,[18] who employed an efficient and accurate intra-auricular manometer capable of recording the pressure variations electrically. They found that PII precedes the rise of intra-auricular pressure only 0.013 to 0.021 second. These figures have practically been confirmed in this laboratory[15] where an average delay of 0.022 second was found for the rise of the intra-auricular pressure recorded by an optical manometer. *The onset of auricular systole thus established as beginning about 0.02 second after the rise of* PII *occurs on the ascending curve or near the summit of* PII (see figure).

Relation to the Phases of Auricular Systole.—Auricular systole is not a simple and united contraction process, but a rapid peristalsis. It has already been pointed out that the excitation wave spreads radially from the sinus node and in its spread excites consecutive portions of the auricle to contract. Receiving its excitation earlier, the auricular tissue near the sinus node begins to contract 0.02 second before the anterior surface of the auricle. Consequently, the anterior portion or body of the auricle does not begin to contract until 0.04 second after the rise of the PII wave; that is, on its descending limb. Not until 0.02 second later, that is, 0.06 second after the rise of PII, is the entire auricle, to judge from the contour of the myogram curve,[15] in a state of contraction. *In short, while the tissue near the sinus node begins to contract 0.02 second after the first rise of* PII, *the tissue near the right auricular appendage does not begin to contract until* PII *has been entirely completed* (see figure).

Relation to the End of Auricular Systole.—When once excited, each fractionate portion of the auricular syncytium continues to contract for an interval of about 0.05 second. Consequently, by the time the most distant portions begin to contract, the more proximal portions are nearing the end of their contraction phase. The total interval that all auricular fibers unite in contracting is consequently very short and

16. Kahn: Arch. f. d. ges. Physiol., 1909, **126,** 197.
17. Lewis: Mechanism of the Heart Beat, London, 1911, p. 24, fig. 13.
18. Garten and Weber: Ztschr. f. Biol., 1915, **66,** 83.

does not exceed *0.015 second*. At the end of this time, that is, *0.075 second* after the rise of PII, the intra-auricular pressure begins to fall and the myogram curve, though still continuing to indicate shortening of the auricular fibers, changes its contour.[15] These facts have been interpreted to mean that the auricular tissue situated near the sinus node has begun to relax. This relaxation process gradually spreads to the more distal portion, but it requires 0.05 second more before a balance between contracting and relaxing units has been reached so that the mass of auricular tissue neither shortens nor lengthens. *From a dynamic point of view it seems desirable to regard this point, which occurs about 0.105 second after the beginning of auricular systole and 0.125 second after the rise of* PII, *as the termination of auricular systole.*

The relation that the termination of auricular systole bears to the RII variation is determined largely by the P-R interval; in a certain measure also by a slight variation in the length of auricular systole. Taking the interval 0.105, referred to in the foregoing, as an average duration, it is evident that if the P-R interval equals 0.125 second, then the end of auricular systole coincides with the beginning of RII. If the P-R interval is shorter than 0.125 second, or if the duration of auricular systole is larger by only a few hundredths of a second (both very common in the dog), then auricular systole extends into the time interval occupied by the R variation (see figure). This means that in such cases the entire auricle still continues to shorten after the excitation wave has spread to the ventricle. On the other hand, if the P-R interval in Lead II is longer than 0.125 second (which is common in man), then auricular systole ends before the R variation by an interval equal to the additional lengthening of this interval.

III. RELATION OF ELECTRICAL VARIATIONS TO VENTRICULAR SYSTOLE

The relation that the electrocardiogram waves bear to the dynamic systole of the ventricle has been investigated by many methods. An extensive review of this subject was given by Kahn[19] in 1914. It is proposed here to reconsider the relation to the ventricular myogram, the intraventricular pressure curve and the heart sounds in the light of recent discoveries.

Relation to Onset of Ventricular Systole.—Most of the earlier experimental evidence favors the idea that the RII variation is practically completed before mechanical systole has begun. Kahn[14] registered the movements of a light needle inserted into the right ventricle synchronously with the electrocardiogram. Ventricular systole so indi-

19. Kahn: Ergebn. d. Physiol., 1914, **14**, 69.

cated began 0.031 to 0.035 second after the rise of RII. A similar delay was shown in the myocardiographic records obtained by Lewis.[17] Previously, Kahn[19] had found that the intraventricular pressure registered by Gad's *Wellenschreiber* began to rise 0.065 second after RII. It must be conceded, however, that the mechanical apparatus employed by these investigators did not qualify to present-day standards, hence the possibility remains that the delay is not inherent in the heart, but is of instrumental origin.

The introduction into experimental work, by Frank, of manometers with a high vibration frequency has stimulated a number of investigators in recent years to compare again the electrocardiogram variations with the intraventricular pressure curves. Piper[20] was the first to report on these relations, but, as his electrogram was led directly from the heart and had a configuration entirely foreign to a normal electrocardiogram, his results were of little apparent value. The question was reinvestigated by Garten[21] who used his electrically recording manometer. He found that the intraventricular pressure began to rise 0.17 to 0.21 second after the beginning of RII; that is, on the ascending limb. This point, it will be recalled, approximately coincides with the end of auricular systole in the dog. In reinvestigating this question by the use of an optical cardiac manometer it has been found in this laboratory that the onset of the pressure rise is uniformly somewhat later; that is, 0.03 to 0.045 second after the initial rise of the RII wave, thus placing the onset of mechanical contraction on the descending limb of the RII wave. The cause of these discrepancies has not been ascertained. It is significant, however, that the RII wave precedes by a short interval the first evidence of mechanical activity in the ventricle.

Relation to End of Ventricular Systole.—The ventricular myogram has been used by Kahn and Lewis to determine the end of ventricular systole. The impression gained from such experiments is that the T variation occurs during the ejection period of the heart, and that a state of iso-potential is reestablished before the onset of ventricular diastole. On account of the involved nature, and, as yet, uncertain interpretation, of any myographic tracing from the ventricles, it is difficult to adjudge the value of such observations. Garten[21] determined the relation of the TII variation to the sudden fall of pressure within the ventricle, and found that a far greater variation exists than in other time relations. Systole, as a rule, terminates 0.034 to 0.048 second after the TII variation; at other times it terminates as much as 0.11 second before the end of T. The end of ventricular systole is not

20. Piper: Centralbl. f. Physiol., 1913, **27,** 392.
21. Garten: Ztschr. f. Biol., 1915, **66,** 23.

always marked sharply, however, on the intraventricular pressure curves. In general, the sudden fall of intra-aortic pressure, designated as the *incisura* by Frank, offers the most exact indication of the termination of ventricular systole. Garten and Wiggers and Dean[22] have established the relation of this event to the T wave. These comparisons agree with the results of Garten in showing the variable relation of the end of systole to the T wave. The significant observation has been made that when the period of systole shortens (for example, after epinephrin), then the T wave becomes broader or remains unaltered, and consequently the end of systole comes appreciably before the T wave has ended. *It is quite evident that the end of ventricular systole cannot be definitely related to any phase of the* TII *variations.*

Relation to the Heart Sounds.—By comparing the recorded heart sounds with the variations of the synchronously recorded electrocardiogram, these relations of the onset and termination of ventricular systole have been confirmed in animals and extended to man. Kahn[23] and Bull,[24] using Weiss' phonoscope, concluded that the first sound vibrations begin 0.03 to 0.04 second after the rise of RII; that is, toward its end. These early attempts to establish electrical and dynamic relations are robbed of much of their significance by the fact that it yet remains to be demonstrated that true sound vibrations can be recorded by this apparatus. The comparison of the sound waves recorded by the phonocardiographic method of Einthoven has given similar results in the hands of Lewis,[25] Fahr[3] and Battaerd,[26] thus confirming the experimental work which places the beginning of ventricular systole on the descending limb of RII.

The issue has been raised, however, whether the first minor vibrations entering into the composition of the first sound are of sufficient intensity to be transmitted to the chest. Fahr[3] found that when special precautions are taken and favorable individuals selected, the main group of vibrations is preceded by one or several "initial vibrations" of small size. If these vibrations constitute the first evidence of ventricular activity, then this dynamic event occurs, according to Fahr, on the ascending limb of RII. This question can be settled only by a direct comparison of the first sound vibrations with the intraventricular pressure curve, which can be accomplished satisfactorily only by recording the fundamental sounds directly from the exposed heart. It has

22. Wiggers and Dean: Am. Jour. Physiol., 1917, **42,** 476.
23. Kahn: Arch. f. d. ges. Physiol., 1909, **129,** 291; ibid., 1910, **133,** 597.
24. Bull: Quart. Jour. Exper. Physiol., 1911, **4,** 289.
25. Lewis: Heart, 1912-1913, **4,** 241.
26. Battaerd: Heart, 1915, **6,** 121.

recently come to my attention that this was attempted by Sinelnikow,[27] who found that the first sound vibration so recorded began precisely with the rise of intraventricular pressure. As this work remains in unpublished form, however, we have no knowledge as to whether the initial or main vibrations are referred to as occurring isochronously with the intraventricular pressure rise. Dean and I,[22] unaware of this unpublished research, carried on similar experiments in which the relation of the various components of the first sound to other cardiac events was analyzed. A specially constructed sound transmitter, stitched to the heart, was connected to a delicate sound recording capsule. It was found that whenever initial vibrations were present they preceded the rise of intraventricular pressure by 0.018 to 0.025 second. The *main vibrations,* however, *are synchronous with the first rise of intraventricular pressure and may be used as an indication of the onset of ventricular systole.*

Similarly, the second sound has been related to the fall of intraventricular pressure and to the incisura of the aortic curve. Sinelnikow, according to Garten, found that the first vibration never occurs until the lowest part of the incisura is reached. Our results, however, give evidence that they coincide precisely with the *beginning* of the incisura. *The second sound vibrations may therefore be used to indicate definitely and accurately the end of systole.*

Applying these results to the combined records of the sounds and electrocardiogram in animals and man, we must conclude that *ventricular systole begins about 0.03 to 0.04 second after the rise of* RII; *that is, on its descending limb, while the end of systole, as indicated in experimental work, bears a variable relation to* TII, *but usually follows the event* (see figure).

IV. SUMMARY AND CONCLUSIONS

In studying the relation between dynamic events and the electrical changes in the heart, it is important that the apparatus utilized to record the several curves at least approximate each other in efficiency and accuracy. This ideal has been attained by the introduction of various types of photographic apparatus, by means of which the dynamic changes in the circulation may be recorded.

The results of such studies show, it is true, minor variations in the relations of dynamic events to the electrical variations recorded by Lead II. These variations are so small, however, that it is possible and desirable to plot on an electrocardiogram the average relation of

27. Sinelnikow: Unpublished experiments referred to by Garten, Ztschr. f. Biol., 1915, **66,** 80.

specific phases of mechanical activity in the auricles and ventricles. This has been done in the curve shown in the figure.

It is not desirable, with our present limited fund of detailed knowledge, to predict the full significance of these relations. A few observations are apparent:

1. No single elevation of the electrocardiogram agrees precisely with the beginning or end of any mechanical event in the auricle or ventricle. The P and R waves, respectively, precede by several hun-

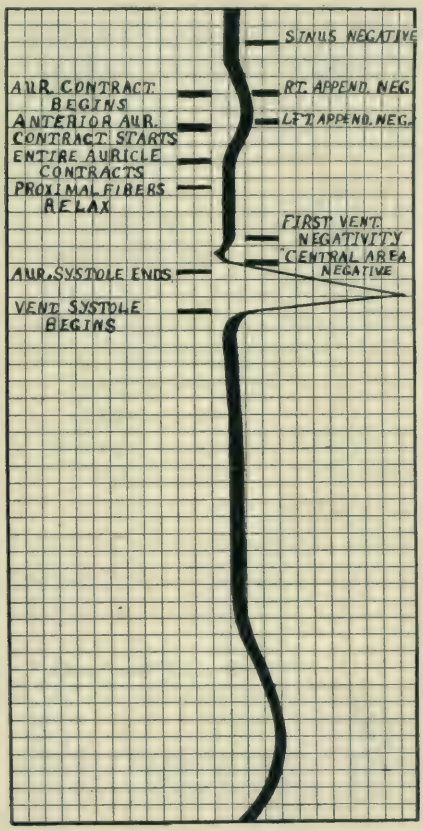


Diagram showing waves of electrocardiogram, Lead II, and their time relations (*a*) to primary negativity of a few regions of heart and (*b*) to mechanical changes in auricles and ventricles when P-R interval equals 0.12 second. Abscissae, 1 division = 0.01 second.

dredths of a second the onset of auricular systole and the beginning of ventricular systole. This observation favors the view that these variations are not associated with the contraction process, but with the propagation of the impulse, across the heart.

2. The end of neither auricular nor ventricular systole is definitely marked on the electrocardiogram. Neither the breadth and duration of the P wave nor the P-R interval are related to the duration of auricular systole; nor is the P-T interval at all a criterion of the duration of ventricular systole. This interval may lengthen when the actual duration of systole has decreased. These observations force us to the conclusion that not only is the amplitude of the electrical variations no criterion of the vigor of contraction, as is well recognized, but the time intervals gleaned from an electrocardiogram cannot be used as a guide to the dynamic functions of the heart. Its clinical value remains restricted to questions dealing with abnormal propagation and initiation of impulses and to conditions producing abnormal axes for the heart. In these fields its value is supreme.

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STUDIES OF THE BLOOD IN BERIBERI*

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I. REFRACTOMETRIC INVESTIGATION OF THE SERUM

Refractometric investigation of the blood was carried out for the first time by Strubell[1] in 1900. He considered the procedure available for measuring the osmotic pressure of the blood, but Reiss,[2] after two years' thorough study of the subject (1901-1902), found that the refractive index bears no relation to osmotic pressure, but that refractometric estimation is practically equivalent to a quantitative determination of protein in the blood. To prove that such a relation exists, Reiss cited a table of results of Vaucher,[3] in which he compared the figures obtained by refraction with those obtained by weighing the proteins.

According to Reiss, the quantity of nonprotein substances in the blood shows no remarkable variation, although the contrary is generally believed to be true. The freezing point of the blood, for example, is normally 0.56 C., and even in extreme cases it does not fall below 0.49, or exceed 0.71. In the case of uremia, however, he notes that the refraction coefficient is influenced by the accumulation of urea and other substances in the blood, and that consequently the refractometric estimation of proteins is, in uremic cases, not reliable.

Strauss,[4] in 1904, used the refractometric method, and it has since been taken up by others.[5] It is now considered by many to be a simple

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* Read before the periodical meeting of the Beriberi Research Committee, 1916.

† A member of the Beriberi Research Committee of the Japanese government.

1. Strubell, A.: Ueber refraktometrische Blutentersuchungen, München. med. Wchnschr., 1902, **49,** 616.

2. Reiss, E.: Die refraktometrische Blutuntersuchung und ihre Ergebnisse f. die Physiologie und Pathologie des Menschen. Ergebn. d. inn. Med., 1913, **10,** 531.

3. Vaucher, E.: L'hydrémie des brightques et des cardiaques oedémateux Paris, 1911.

4. Strauss, H.: Demonstration der refraktometrischen Blutuntersuchung, Deutsch. med. Wchnschr., 1905, **31,** 83.

5. Neuberg, C.: Der Harn. Berlin, 1911; Tranter, C. L., and Rowe, A. H.: The Refractometric determination of Albumin, Globulin, and Nonprotein in Normal Human Blood Serum, Jour. Am. Med. Assn., 1915, **65,** 1433; Legueu, E.: Nutzen der Anwendung der Harnstoffsekretionskonstante bei den Prostatikern, Berl. klin. Wchnschr., 1913, **50,** 1741.

and convenient method for the estimation of the protein content of the serum.

The present article gives the results of a recent refractometric investigation of the serum of beriberi patients in the Tokyo Municipal Charity Hospital. Abbe's *Universalrefraktometer* was used for the experiments, as Pulfrich's *Eintauchrefraktometer,* which is generally recommended, was not available.

We recognized the desirability of taking the blood at a definite time each day, owing to the influence of the ingestion of food on the protein content, but as all of the patients examined were outpatients, it was

TABLE 1.—VAUCHER'S COMPARISON OF REFRACTOMETRIC AND WEIGHT METHODS OF BLOOD PROTEIN ESTIMATION

Number or Species	Refraction, per Cent.	Weight, per Cent.
HUMAN SERUM		
I	8.82	8.79
II	8.5	8.49
III	9.41	9.417
IV	8.11	8.12
V	9.2	8.192
ANIMAL SERUM		
Ox	8.15	8.14
Ox	8.4	8.384
Horse	8.31	8.28
Pig	7.88	7.85
Pig	8.63	8.58

not always possible to observe this rule. We fixed the time at 11 a. m. and took the blood as near that time as possible. The blood was received in a capillary tube and put into a refrigerator until coagulation had taken place. Any serum which was found to be tinged with red was discarded. A temperature of 17.5 C. was maintained by means of the regulator connected with the apparatus. The examinations were made almost exclusively on recently admitted patients, since the use of aperients, such as sulphate of magnesia, is thought to increase somewhat the concentration of the blood.

The results of our examinations may be tabulated as shown in Table 2.

TABLE 2.—AUTHORS' ESTIMATIONS

No.	Name	Sex*	Age	Length of Time between Onset and Examination	Refractive Index	Protein, per Cent.
1	Y. Z.	♂	24	1 month	1.3540	10.4
2	N. M.	♂	..	.....	1.3539	10.4
3	O. H.	♂	18	.....	1.3526	9.5
4	Y. M.	♂	19	10 days	1.3525	9.5
5	H. M.	♂	19	5 to 6 days	1.3515	9.1
6	F. K.	♂	22	5 to 6 days	1.3515	9.1
7	S. M.	♂	23	3 weeks	1.3512	8.9
8	N. Y.	♂	56	4 months	1.3510	8.8
9	T. T.	♂	55	3 weeks	1.3505	8.5
10	Y. T.	♂	29	3 months	1.3498	8.1
11	S. R.	♂	20	20 days	1.3498	8.1
12	K. N.	♂	20	.....	1.3488	7.5
13	O. T.	♂	37	.....	1.3485	7.4
14	K. T.	♂	43	4 months	1.3477	6.8
15	M. T.	♂	27	.....	1.3475	6.8
16	F. S.	♂	54	1 month	1.3472	6.6
17	M. T.	♂	51	.....	1.3470	6.5
18	T. S.	♂	16	1 week	1.3468	6.3
19	T. S.	♂	[illegible]	.....	1.3465	6.1
20	Y. S.	♀	24	2 weeks	1.3520	9.4
21	S. K.	♀	28	2 weeks	1.3517	9.2
22	S. T.	♀	41	1 month	1.3506	8.6
23	S. K.	♀	61	1½ months	1.3502	8.4
24	O. K.	♀	29	1 month	1.3500	8.2
25	S. K.	♀	20	5 to 6 days	1.3499	8.2
26	S. S.	♀	23	.....	1.3495	7.9
27	Y. T.	♀	43	6 months	1.3495	7.9
28	H. I.	♀	34	2 months	1.3495	7.9
29	I. Y.	♀	22	1 month	1.3493	7.8
30	K. T.	♀	42	1 week	1.3489	7.6
31	K. I.	♀	[illegible]	40 days	1.3489	7.6
32	A. T.	♀	24	5 to 6 days	1.3486	7.4
33	I. N.	♀	47	.....	1.3480	7.0
34	S. M.	♀	41	2 months	1.3479	7.0

* ♂ = male; ♀ = female.

As the table shows, the quantity of protein in the serum of thirty-four patients with beriberi, as computed from the refractive index, varied from 6.1 to 10.4 per cent. For purposes of comparison, we give, in Table 3, the results of several other authors.

TABLE 3.—Refractometric Estimatlons of Other Authors for Comparison

Author	Refractive Index	Protein, per Cent.
Reiss	1.34802–1.35145	7.0–9.0
Strauss, Chajes	1.3480 –1.3510	7.0–8.7
Engel	1.3487 –1.3522	7.4–9.4
Martins	1.3480 –1.3520	7.0–9.0
Goldammer	1.34724–1.35169	6.6–9.1
Böhme	1.3476 –1.3512	6.8–8.9
Winternitz	1.34940–1.35058	7.8–8.5
Widal, Bernard, Vaucher	1.34904–1.35042	7.6–8.4
Tranter, Rowe	.....	6.7–8.7

TABLE 4.—Serum of Healthy Persons

Number	Name	Sex*	Age	Refractive Index	Protein, per Cent.
1	O. C.	♂	20	1.3507	8.6
2	Y. K.	♂	36	1.3483	7.2
3	H. I.	♂	32	1.3483	7.2
4	I. K.	♂	56	1.3477	6.9
5	Y. M.	♂	10	1.3476	6.8
6	M. T.	♂	34	1.3473	6.6
7	T. N.	♂	21	1.3469	6.4
8	T. Z.	♂	30	1.3468	6.3
9	I. C.	♀	17	1.3490	7.6
10	M. S.	♀	68	1.3486	7.4
11	K. T.	♀	43	1.3479	7.0
12	T. F.	♀	16	1.3478	6.9
13	Y. T.	♀	30	1.3475	6.8
14	O. H.	♀	28	1.3469	6.4
15	K. F.	♀	17	1.3468	6.4

* ♂ = male; ♀ = female.

The figures for protein content in Table 3 vary from 6.6 to 9.4 per cent. If we assume that the normal protein content is found between 6.6 and 9.4 per cent., then the protein content of the beriberi blood

examined conformed in half the cases with the minimum normal figure but in the other half considerably exceeded the maximum normal figure. We examined as controls the serums of fifteen healthy Japanese. The results are given in Table 4.

The number of persons examined as controls was not large enough to warrant our accepting the figures obtained as representing the standard in healthy persons, yet it seems probable that the standard approaches these figures. A comparison of the figures in Table 4 with those of Table 2 apparently shows that the refractive index of the serum of persons suffering from beriberi is in general higher than that of normal persons. From Table 5, in which the average amount of protein for healthy and for beriberi serum is compared, it is clear that the quantity of protein in beriberi serum is greater than that of normal serum, irrespective of sex.

TABLE 5.—Comparison of Serums from Normal Persons and Beriberi Patients

	Average in Male, per Cent.	Average in Female, per Cent.	Total Average, per Cent.
Healthy serum	7.0	6.96	6.92
Beriberi serum	8.11	8.06	8.01

SUMMARY

The investigation reported in the foregoing account was made on the assumption that the rise in the refractive index of the serum in beriberi is dependent only on the increase of its protein content. It is possible, however, that it is also due to the retention of nonprotein substances. We may state in conclusion that the refractive index of the serum of persons suffering from beriberi shows often no deviation from the normal, but not infrequently a marked rise.

II. DETERMINATION OF UREA IN THE BLOOD AND OF AMBARD'S COEFFICIENT

Urea in the Blood.—Although the elimination of urea in beriberi has frequently been the subject of study, so far no results of studies on urea in the blood in these cases have been reported. The reason is probably that for ordinary methods a comparatively large quantity of blood is required. Moreover, the necessarily complicated technic makes such study impracticable. Both of these obstacles are removed,

however, in the method of determination of urea in the blood by means of urease reported by Van Slyke, Zacharias, and Cullen[6] in 1914.

The results reported in the present paper were obtained by estimations of urea in the blood, according to the urease method, of both inpatients and outpatients of the Tokyo Municipal Charity Hospital. The urease was prepared by Bertrand's method, because in a preliminary comparison of samples of urease prepared (*a*) by the method of Hahn and Saphra,[7] (*b*) by the method of Van Slyke, Zacharias, and Cullen,[6] and (*c*) by Bertrand's method,[8] the urease prepared by the latter method was found most active. The determination of the quantity of urea, however, was made after Hahn and Saphra, because their method was simplest. The blood was taken from inpatients

TABLE 6.—Amount of Urea in Beriberi Blood

Outpatients								Inpatients			
No.	Name	Sex†	Urea, per Mille	No.	Name	Sex†	Urea, per Mille	No.	Name	Sex†	Urea, per Mille
1	A.	♂	0.2	12	M.	♂	0.4	23	U.	♂	0.23
2	K.	♂	0.3	13	S.	♂	0.41	24	O.	♂	0.24
3	A.	♂	0.3	14	Y.	♂	0.42	25	O.	♀	0.25
4	M.	♂	0.32	15	K.	♂	0.45	26	S.	♂	0.28
5	K.	♂	0.32	10	M.	♂	0.46	27	O.	♀	0.29
6	T.	♀	0.32	17	H.	♂	0.49	28	S.	♀	0.30
7	O.	♂	0.32	18	K.	♂	0.50	29	O.	♂	0.33
8	S.	♂	0.34	19	K.	♂	0.50	30	H.*	♂	0.45
9	O.	♂	0.36	20	M.	♂	0.52	31	A.*	♂	1.03
10	F.	♂	0.37	21	O.	♂	0.6	32	H.*	♂	1.1
11	K.	♂	0.38	22	S.	♀	0.6	33	K.*	♂	5.79

* These patients were severe cases. A. and K. died from cardiac failure, not infrequent in beriberi. The remaining two were discharged after gradual recovery.
† ♂ = male; ♀ = female.

before breakfast and from outpatients at 11 a. m. The results are given in Table 6.

The quantity of urea in the twenty-two outpatients varied from 0.2 to 0.6 gm. per liter, an average of 0.3 to 0.4 being general. In the seven mild house cases, the quantity varied from 0.23 to 0.33 gm. per

6. Van Slyke, D. D., Zacharias, G., and Cullen, G. E.: Die Darstellung fester Urease und ihre Verwendung zur quantitativen Bestimmung von Harnstoff im Harn, Blut, und in der Zerebrospinalflüssigkeit, Deutsch. med. Wchnschr., 1914, **40,** 1219.

7. Hahn, A., and Saphra, J.: Ein einfache für die Praxis geeignete Methode zur quantitativen Bestimmung des Harnstoffs im Urin, Deutsch. med. Wchnschr,, 1914, **40,** 430.

8. Bertrand: Practical Physiological Chemistry (Japanese translation).

liter. Three out of four severe house cases showed a considerable retention of urea — 5.79 gm. per liter in one case.

Table 7 gives the figures obtained by several workers for determinations of urea in healthy blood.

Apparently, then, the normal amount of urea in the blood varies from 0.2 to 0.6 gm. per liter. One of us (Nemoto) obtained practically the same figures (0.2 to 0.56 gm. per liter) from twenty-one patients without renal disease and two healthy persons. As shown in Table 6, the urea content of the blood in mild cases of beriberi was within normal limits, but in severe cases it not only increased to more than 1.0 gm. per liter, but in one case rose beyond 5.0 gm. per liter. This case recalls one reported by M. Miura[9] several years ago, in which he estimated 5.0 gm. per liter of urea in the pleural and peritoneal effusion from a case of beriberi. Miura, however, did not estimate the urea in the blood. Such a deviation from the normal appearing in severe cases may be due to a combination of two causes: (1) lessened elimination of urine as a result of weakened heart action, and (2) increased protein metabolism (K. Miura, Y. Teruchi, and others), but which of these two is the main cause cannot be stated without further study.

TABLE 7.—Quantity of Urea in Healthy Blood

Author	Urea, Gm. per Liter	
Schöndorff	0.23-0.505	
Schöndorff	1.5	(After the intake of a large quantity of protein)
Jaksch	0.3-0.6	
McLean	0.2-0.5	(Estimated with urease)

Ambard's Coefficient.—Ambard's law with regard to kidney function has been confirmed by several workers. The details of the subject are well known and will not be recounted here. Ambard has reported that the coefficient in healthy persons ranges from 0.06 to 0.07, and that the coefficient is higher as the deviation in kidney function is greater. McLean,[10] who used urease for the determination of urea in his study of the subject, suggests 0.08 as the coefficient in healthy persons.

The results obtained by us with cases of beriberi are as shown in Table 8.

9. Miura, K.: Beriberi, 1913.

10. McLean, F. C.: The Numerical Laws Governing the Rate of Excretion of Urea and Chlorid in Man. I. An Index of Urea Excretion and the Normal Excretion of Urea and Chlorid. II. The Influence of Pathological Condition and of Drugs on Excretion, Jour. Exper. Med., 1915, **22**, 212, 366.

Ambard's coefficient ranged from 0.07 to 1.36, and in the majority of cases was above 0.09. If we take 0.08 as the normal coefficient — and our controls confirm McLean's results — then the coefficient in beriberi cases is greater than the normal. The rise of the coefficient does not necessarily coincide with the severity of clinical manifestations, for some mild cases showed a coefficient of 0.13 or 0.14, and some severe cases 0.07 or 0.08. It appears that in comparatively mild cases the function excreting urea may be disturbed, while in severe cases it may not be affected. It is worthy of note that in two out of four severe cases which showed a normal coefficient the patients afterward recovered, while the two patients who had a high coefficient died.

TABLE 8.—AMBARD'S COEFFICIENT IN BERIBERI CASES

No.	Name	Nature of Case	Wt., Kg.	Urine, 24 Hrs.		Urea in Blood, Gm. Liter	Urea in Urine, per Cent.	Coefficient	Remarks
				C.c.	Gm.				
1	K.	Severe	60	1,350	18.79	5.79	13.91	1.36	Died
2	A.	Severe	60	1,410	40.25	1.03	28.46	0.14	Died
3	H.	Severe	40	3,020	105.92	1.10	35.09	0.08	Recovered
4	H.	Severe	52	1,605	32.28	0.45	20.11	0.07	Recovered
5	S.	Mild	36	1,550	6.51	0.30	4.20	0.14	Recovered
6	O.	Mild	51	384	8.91	0.29	23.21	0.08	Recovered
7	O.	Mild	42	840	6.92	0.33	8.23	0.13	Recovered
8	U.	Mild	41	624	4.77	0.23	7.64	0.10	Recovered
9	O.	Mild	36	864	8.05	0.25	9.31	0.09	Recovered
10	O.	Mild	49	1,728	13.27	0.24	7.68	0.08	Recovered
11	S.	Mild	54	1,152	12.40	0.28	10.76	0.09	Recovered
C*	M.	Normal	53	792	10.95	0.25	13.82	0.08	
C*	K.	Normal	48	1,066	14.11	0.27	12.01	0.08	

* Control.

These instances seem to suggest that the cardiac failure in beriberi may be due to uremia, yet the clinical symptoms in cases of cardiac failure in beriberi are quite different from those of the ordinary uremia. It is possible that in beriberi some unknown toxic substances are produced in the blood which, if excreted in the same manner as urea, do not cause death, but the accumulation of which in the blood causes heart failure. If this is true, then it is conceivable that the amelioration of the threatening symptoms of beriberi which venesection brings is the result of diminution of the unknown toxic products. Further investigation of this subject is necessary before a definite statement can be made.

SUMMARY

1. The quantity of urea in the blood of beriberi patients shows, in mild cases, no deviation from the normal, but in the majority of severe cases a marked increase.

2. Ambard's coefficient is not infrequently higher than normal in beriberi; that is, the function excreting urea is frequently disturbed.

3. The disturbance of the kidney function does not necessarily coincide with the gravity of the clinical manifestations.

4. Even in cases in which the clinical symptoms are severe, if the function excreting urea is intact, the prognosis is hopeful.

5. It is possible that cardiac failure in beriberi is due to an accumulation of some unknown toxic products in the blood, the elimination of which is coincident with the elimination of urea.

A STUDY OF RENAL FUNCTION IN PATIENTS CONVALESCING FROM ACUTE FEVERS*

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The newer methods of functional kidney examination make it possible to secure evidence of renal disturbance formerly not obtainable. In grave and advanced forms of acute and chronic nephritis this information has proved its value. In the borderline cases, the milder disturbances of the kidney often unrevealed by older methods, we would expect functional tests to be of still greater aid in diagnosis and prognosis.

The slight albuminuria of the acute infectious fevers, often accompanied by hyaline casts and commonly disappearing with the fever, may be taken as a type of the disturbances referred to. A sharp line has usually been drawn between this "febrile albuminuria" and true nephritis. It is the common impression that this accompanying albuminuria, if it disappears with or shortly after the fever, is accompanied by no important renal change and is never of serious import.

It appears of value at this time to consider the effect of the acute fevers and of febrile albuminuria on renal function, and if we find that this is disturbed, to inquire how long the impairment lasts. We should gain in this way a truer estimate than was heretofore possible of the importance of the renal syndrome in the subsequent history of the individual.

For these reasons the functional tests here reported were made on patients during or after convalescence from acute fevers. In all but two of the patients studied, and these are included mainly for comparison, the effect of the fever on the kidneys, judged from the clinical symptoms and the ordinary clinical urine examination during the fever, was either none at all or the production merely of a mild febrile albuminuria. One patient, however, had edema of the face and extremities, with slight urinary changes, several weeks after a tonsillitis. Another had a prolonged fever due to a staphylococcus meningitis. During the fever there was a distinct nephritis, but the urine had been normal for

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a month before the tests were made. In most of the other patients the urine had been normal a number of days before the tests.

The tests were made, as a rule, shortly before the patient left the hospital, and from three to fifteen days after the temperature had become normal. In only two cases was it possible to follow the patient after discharge. The results of the estimation of phenolsulphonephthalein excretion and of the examination of two-hour specimens of urine after a test diet as outlined by Dr. Mosenthal[1] are of especial interest. In estimating the degree of impairment, the standards recently given by Mosenthal and Lewis[2] have been used. In Table 16 the results are summarized, slight impairment being denoted by figures in parentheses, moderate impairment by heavy faced type.

Over one-half of the patients had some degree of nocturnal polyuria. This was seldom of a high grade. There are no reports from other sources in regard to this criterion of renal function in cases similar to those herein reported. In indicating impaired kidney function, it is, however, of undoubted value.

The changes shown in the two-hour phthalein excretion are most striking, and but few other observations could be found in similar conditions.

Rowntree and Geraghty,[3] during typhoid fever, found an excretion of 45.5 per cent. In a fatal case of pneumonia with gangrene they reported an excretion of 57 per cent., and a similar case examined by Thayer and Snowden[4] there was an elimination of 27 per cent., and again 20 per cent. of the dye in two hours. At necropsy the changes in the kidneys were similar in both, one showing a "fatty degeneration" and the other "cloudy swelling." Incidental to their study of renal function in serum disease, Longcope and Peters[5] studied the phthalein excretion in a few cases of pneumonia. Before crisis they found in one case 26 per cent. and later 50 per cent.; in another 56 per cent., and after crisis in the same patient 51 per cent. Another patient after crisis eliminated 64 per cent.

Observations published by Lewis[6] while this paper was in preparation are of especial interest. He finds a marked increase (average excretion 70.5 per cent.) common to all fevers. This is associated with increased functional activity of the kidneys as evidenced by an enormous increase in the rate of output of urea. Determinations made after the temperature had been normal for four days showed a marked

1. Mosenthal, H. O.: The Archives Int. Med., 1915, **16,** 733.
2. Mosenthal and Lewis: Jour. Am. Med. Assn., 1916, **67,** 933.
3. Rowntree and Geraghty: The Archives Int. Med., 1912, **9,** 284.
4. Thayer and Snowden: Am. Jour. Med. Sc., 1914, **148,** 781.
5. Longcope and Peters: The Archives Int. Med., 1916, **18,** 496.
6. Lewis: The Archives Int. Med., 1917, **19,** 1.

return to normal of both urea and phthalein output, the latter averaging 63 per cent. Determinations of phthalein output during convalescence were made by him on three patients with typhoid fever and were as follows:

Case	Days after Fever	Two-Hour Dye Excretion Per Cent.
409	During fever	68
	20	59
	60	65
	6 months	69
411	During fever	78
	7	81
416	6	50

In general, then, previous observations show a certain amount of disturbance of phthalein excretion during fever, while observations during convalescence are too scanty to justify any generalizations.

Of our fifteen patients, only three had a phenolsulphonephthalein excretion of over 60 per cent. One of these, Case 15, is the same patient convalescent from a meningitis to whom reference has previously been made and who undoubtedly had a chronic nephritis. In five instances the concentration was well below 40 per cent., the lowest being 27 per cent. In one patient there was hyperpermeability for the dye, the excretion being 88 per cent. (Case 3).

On the test diet, fixation of the specific gravity of the two-hour specimens was noted only once — in a young man (Case 10) recovering from pneumonia, who, in childhood, had had scarlet fever. In three patients (Cases 3, 10 and 15) there was an indication of fixation of the quantity of the two-hour specimens. One of these was the meningitis patient (Case 15), whose urine during the fever period indicated a true nephritis.

Most of the patients had a normal concentration of salt in the two-hour specimens. In three cases (5, 7 and 11) it was somewhat lowered. Our observations, however, bring out some suggestions of interest in the chlorid metabolism, though they cannot, of course, be regarded as giving accurate balances.

It has been shown repeatedly by others that there is retention of chlorids during the course of acute fevers, and that this is followed by an increased elimination during convalescence. These changes are extreme in pneumonia. But in malaria, during the paroxysm, chlorid excretion is greatly increased. In most of the patients a chlorid deficit, or at least an approximate balance, was therefore to have been expected. On the Mosenthal test diet in normal controls the sodium chlorid in the urine for the twenty-four-hour period about equals or exceeds the intake. Many of the patients, we must assume, had for elimination sodium chlorid stored up during the fever, in addition to that contained in the food. Yet we find that most of them excreted

considerably less even than their intake of approximately 9.0 gm. This does not agree with the increased elimination of chlorids after fever, which many other observers have found. Most of our patients certainly retained salt during the test. This may be due in part to diminished kidney efficiency, or it may be associated with the gain in weight which takes place during convalescence. To decide on the importance of the former factor it would have been valuable to observe the manner of excretion of salt added to the diet.

A low, fixed salt concentration, it is well known, is one of the early signs of kidney impairment. It is my impression that lowered kidney function is at least partly responsible for the very marked retention and the low concentration of salt in the urine during the fever of pneumonia, because not only is the salt concentration low at this stage, but also, as von Moraczewski[7] has shown, there is scarcely any increase in the excretion, if 5 or 10 gm. are added to the food. If this low concentration during the fever is due, as seems likely, to the inability of the kidney to excrete salt in higher concentration, one would expect to find some indication of this lowered power during convalescence as well, such as our patients show.

In the blood, incoagulable nitrogen and urea nitrogen were determined. No striking changes were found. The great destruction of nitrogenous bodies which takes place during fever makes the interpretation of slight changes difficult. These findings are therefore given without discussion. Uric acid was estimated in two patients, and in both the amount in the blood was moderately elevated. Both patients showed other signs of renal disturbance. More information as to this factor would be of interest in view of the conclusion of Myers and Fine,[8] that in chronic nephritis, uric acid is the first of the nitrogenous bodies to show an increase in the blood. Its increase in gout they also ascribe to renal disturbance. The finding of increased amounts after fever suggests that it would be of interest to investigate to what extent the accumulation in gout depends on the fever of the acute attacks.

METHODS

Phenolsulphonephthalein Test: Technic of Rowntree and Geraghty.[9]

Blood: 1. Urea: Van Slyke and Cullen's modification of Marshall's method.[10] 2. Incoagulable Nitrogen: Greenwald.[11] 3. Uric Acid: Dr. T. Kuttner's microcolorimetric modification of the Folin method (about to be published).

7. Von Moraczewski: Ztschr. f. klin. Med., 1900, **39,** 44.

8. Myers and Fine: Jour. Biol. Chem., 1915, **20,** 931; also Chase and Myers: Jour. Am. Med. Assn., 1916, **67,** 929.

9. Rowntree and Geraghty: The Archives Int. Med., 1912, **10,** 284.

10. Van Slyke and Cullen: Jour. Biol. Chem., 1914, **19,** 211.

11. Greenwald: Jour. Biol. Chem., 1915, **21,** 61.

Test Diet: The technic followed closely that described by Dr. Mosenthal. The diet employed was analyzed repeatedly. The nitrogen content was about 13.7 gm. The salt content varied somewhat and averaged about 9.0 gm. The diet was, as a rule, given for two days instead of one, and the specimens were collected on the second day.

The following table, extracted from one given by Mosenthal and Lewis,[3] is useful for interpretation of results.

SCALE OF IMPAIRMENT OF RENAL FUNCTION AS INDICATED BY TESTS EMPLOYED

Degree of Impairment of Renal Function	Phenolsulphonephthalein Per Cent.	Test Meal for Renal Function			
		Night Urine		Variation in Sp. Gr. When the Highest is	
		c.c.	Sp. Gr.	1.018	1.017-1.015
Normal —	60+	400	1.018+	9+	
Slight +	59-40	401-600	1.016 and 1.017	8-5	6+
Moderate ++	39-25	601+	1.015	4	5 and 4
Marked +++	24-11	.....	.....	.....	3
Maximal ++++	10-0				

DISCUSSION

Prognostic Considerations.—In considering the results of tests of renal function one cannot emphasize too much that they yield no absolute conclusions as to the kind and degree of histologic damage the kidneys have sustained. This was brought out by Schlayer[12] early in the modern study of renal physiology. Severe functional impairment may be transitory, or it may be dependent on factors outside the kidney. Severe histologic damage may or may not be attended by functional disturbance of the same degree, but it is likely to persist. If the functional tests could have been repeated in my patients at intervals after convalescence, many of the changes would have been seen to disappear quickly. If this were not the case, one would have to assume that in most individuals a nocturnal polyuria and a lowered phthalein index are permanent after acute fevers. Persistance of such changes would certainly indicate a chronically damaged kidney. There is a suggestion of such damage in Case 8, months after the original disease; while in Case 15 the kidneys evidently failed to recover their normal functional capacity.

On the other hand, it is clear that functional tests will often reveal a nephritis which would not be recognized by other methods of examination. Absence of albumin and casts after fever is not a guarantee that the kidneys are normal. Case 15 again shows this in a striking manner. Febrile albuminuria, I believe, is usually dependent on an actual nephritis, and my results justify the conclusion that the albumin disappears long before the kidneys have recovered completely. It is clear from this that recovery can best be gaged by repeating functional tests at intervals during and after convalescence. It is probable that in this way a chronic nephritis will not rarely be found to date back to some apparently trifling febrile albuminuria.

12. Schlayer: z. Med. Klin., Beiheft., 1912, **8**, 211.

Diagnosis.—In this series the phthalein test showed a much more apparent disturbance than the other methods employed. This is contrary to the results usually obtained in chronic nephritis,[13] in which the dietetic test usually shows disturbance much earlier than the other methods. Dye excretion as low as 27 per cent. was found with kidneys which clinically must be pronounced sufficient. In a nephritic patient such values are usually accompanied by nitrogen accumulation in the blood, and are of serious import.[14] In the absence of cumulative phenomena and of other confirmatory clinical evidence, extreme caution is therefore to be exercised in concluding from lowered phthalein excretion that the kidneys are seriously diseased. This is true, especially in patients who have recently had an acute febrile disease, even though other functional tests give some confirmatory evidence.

In chronic nephritis the same care is needed in the interpretation of results. Here one would expect fever to disturb function even more than in normal individuals. Under these circumstances a high degree of impairment of kidney efficiency might well be temporary, and a bad prognosis based mainly on functional tests would often prove fallacious.

SUMMARY AND CONCLUSIONS

Renal functional tests carried out on a series of patients after acute fevers lead to the following conclusions:

1. Without other signs of nephritis, most of them showed distinctly impaired function.
2. The greatest disturbance was shown by the phenolsulphonephthalein test.
3. Nocturnal polyuria was also frequent, though usually slight.
4. In interpreting the results of functional renal tests, the influence of a preceding febrile disease must always be considered.

The prognostic and diagnostic importance of these facts is discussed.

The influence of fever on the concentration of uric acid in the blood and on the ability of the kidneys to concentrate sodium chlorid is discussed.

REPORTS OF CASES

CASE 1.—(163621.) Abraham F., aged 30. Previous history of no importance. Takes two drinks of whiskey a day.

Present illness, acute lobar pneumonia; temperature normal after May 20; blood pressure, systolic 110, diastolic 55.

Urine: Twenty-four-hour specimens, specific gravity, 1.010 to 1.030; albumin, a trace occasionally found, and in three of twelve specimens a few granular casts; quantity 650 to 1,500 c.c.

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13. Mosenthal: Jour. Am. Med. Assn., 1916, **67,** 933; Christian, H. A.: discussion, ibid.
14. Elliott, A. R.: Jour. Am. Med. Assn., 1915, **64,** 1885.

TABLE 1.—Data of Renal Function in Case 1

May 26, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	135	1.026	1.02	1.38	1.62	2.19
10 to 12 a. m.	55	1.029	0.85	0.47	1.74	0.96
12 to 2 p. m.	65	1.031	1.0	0.65	2.4	1.56
2 to 4 p. m.	100	1.030	1.11	1.11	1.4	1.4
4 to 6 p. m.	70	1.027	1.0	0.7	1.43	1.0
6 to 8 p. m.	100	1.026	0.82	0.82	1.68	1.68
Total day	525	.....	0.97	5.13	....	8.79
8 p. m. to 8 a. m.	415	1.019	0.62	2.57	1.04	4.32
Total 24 hours	940	.....	0.82	7.7	....	13.11

Blood: May 23, incoagulable nitrogen, 56 mg. per 100 c.c.; urea nitrogen, 30 mg. per 100 c.c.

Phthalein elimination May 23, per cent., first hour, 25; second hour, 19; two-hour total, 44.

Summary: Water retention; slight nocturnal polyuria; definitely impaired dye excretion.

Case 2.—(163220.) Abraham W., aged 14. No previous illness. Acute lobar pneumonia lasting ten days. Crisis May 3. Blood Pressure, May 1, systolic 100, diastolic 60.

Urine: Twenty-four-hour specimens, quantity, 700 to 1,400 c.c.; acid; specific gravity, 1.020 to 1.028; albumin, +; hyaline casts repeatedly until crisis, then normal.

TABLE 2.—Data of Renal Function in Case 2

May 10, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	225	1.007	0.25	0.56	0.46	1.04
10 to 12 a. m.	150	1.022	0.29	0.44	1.07	1.6
12 to 2 p. m.	65	1.026	0.51	0.33	1.54	1.0
2 to 4 p. m.	70	1.026	0.7	0.49	1.26	0.88
4 to 6 p. m.	85	1.023	0.48	0.41	1.85	1.57
6 to 8 p. m.	70	1.026	0.33	0.23	1.36	0.95
Total day	665	.....	0.37	2.46	....	7.04
8 p. m. to 8 a. m.	375	1.024	0.78	2.93	1.54	5.78
Total 24 hours	1,040	.....	0.51	5.39	....	12.82

At dinner, failed to take soup, green vegetable and half the bread and butter.

Phthalein elimination May 11, per cent., first hour, 16; second hour, 22; two-hour total, 38.

Summary: Retention of salt and water; moderately impaired dye excretion.

Case 3.—(161488.) Israel E., aged 18. Previous history, no infectious diseases; frequent headaches.

Present illness, acute lobar pneumonia; crisis February 22. February 20, blood pressure, systolic 108, diastolic 55.

Urine: Single specimens, specific gravity, 1.019 to 1.024; albumin, faint trace during fever; none later; microscopically negative.

Blood: March 1, incoagulable nitrogen, 47 mg. per 100 c.c.; urea nitrogen, 14 mg. per 100 c.c.

TABLE 3.—Data of Renal Function in Case 3

March 2, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	210	1.008	0.25	0.52	0.5	1.05
10 to 12 a. m.	220	1.009	0.26	0.57	0.45	1.0
12 to 2 p. m.	180	1.016	0.51	0.92	0.67	1.2
2 to 4 p. m.	210	1.013	0.44	0.93	0.57	1.19
4 to 6 p. m.	190	1.014	0.44	0.84	0.72	1.37
6 to 8 p. m.	110	1.017	0.39	0.43	0.94	1.03
Total day	1,120	.....	0.37	4.21	....	6.84
8 p. m. to 8 a. m.	510	1.017	0.74	3.77	1.02	5.2
Total 24 hours	1,630	....	0.48	7.98	....	12.04

Phthalein elimination, per cent., first hour, 50; second hour, 38; two-hour total, 88.

Summary: The total water output and the night urine are increased. Salt concentration is low. The variation in specific gravity is nine points—just within normal limits. The value of these results is lessened because the dye test with its increased fluid intake seems to have been done on the same day as the urinary test meal. Dye excretion is increased.

Case 4.—(162451.) Harry T., aged 14. Previous history, scarlet fever in early childhood. One brother has kidney trouble.

Present illness, acute lobar pneumonia lasting seven days; fever until April 2. Blood pressure, April 3, systolic 115, diastolic 60.

Urine: Repeated examination of twenty-four hour specimens, quantity, 700 to 1,000 c.c.; specific gravity, 1.028 to 1.030; albumin, faint trace; microscopically, once a few granular casts found; no casts in the remaining specimens.

TABLE 4.—Data of Renal Function in Case 4

April 11, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	225	1.016	0.7	1.57	0.98	2.2
10 to 12 a. m.	80	1.021	0.73	0.58	1.07	0.86
12 to 2 p. m.	165	1.014	0.73	1.2	0.66	1.09
2 to 4 p. m.	135	1.020	1.08	1.46	0.82	1.1
4 to 6 p. m.	225	1.012	0.55	1.24	0.61	1.37
6 to 8 p. m.	70	1.023	0.62	0.43	1.35	0.95
Total day	900	.....	0.72	6.48	....	7.57
8 p. m. to 8 a. m.	200	1.028	0.78	1.56	1.68	3.36
Total 24 hours	1,100	.....	0.73	8.04	....	10.93

Phthalein elimination, per cent., first hour, 9.5; second hour, 30; two-hour total, 39.5.

Summary: Normal response to test diet; dye excretion moderately impaired.

Case 5.—(162588.) Morris G., aged 32. Previous history, scarlet fever at 2 years; takes about two drinks of whiskey daily.

Present illness, acute lobar pneumonia lasting fourteen days.

Urine: Examination of single specimens, specific gravity, 1.018 to 1.024; albumin present; a few granular casts found occasionally during fever and once during convalescence.

Blood: April 23, incoagulable nitrogen, 53.9 mg. per 100 c.c.; urea nitrogen, 10.5 mg. per 100 c.c.; uric acid, 4.5 mg. per 100 c.c.

TABLE 5.—Data of Renal Function in Case 5

April 22, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	240	1.009	0.39	0.94	0.61	1.46
10 to 12 a. m.	40	1.015	0.64	0.25	0.63	0.25
12 to 2 p. m.	220	1.010	0.37	0.81	0.46	1.0
2 to 4 p. m.	30	1.013	0.62	0.19	0.56	0.17
4 to 6 p. m.	200	1.012	0.48	0.96	0.54	1.08
6 to 8 p. m.	55	1.015	0.41	0.22	0.64	0.36
Total day	785	.....	0.43	3.37	....	4.33
8 p. m. to 8 a. m.	640	1.013	0.33	2.11	0.69	4.42
Total 24 hours	1,425	.....	....	5.48	....	8.75

Phthalein elimination, April 23, per cent., first hour, 40; second hour, 15; two-hour total, 55.

Summary: The microscopic examination of the urine shows a slight nephritis. After the test diet the specific gravity is low and the variations are below normal. There is a tendency to fixation in concentration of salt and of nitrogen. The night urine shows moderate increase in amount, low salt and nitrogen concentration; dye excretion slightly impaired.

Case 6.—(161930.) George S., aged 32. Previous history; typhoid fever in childhood.

Present illness, acute lobar pneumonia lasting nine days, with icterus. Crisis March 18. From April 1 to 9, slight fever again with a macular rash; diagnosis doubtful. Blood pressure, April 11, systolic 80, diastolic 45.

Urine: Twenty-four-hour specimens, specific gravity, 1,014 to 1.022; quantity, 700 to 1,100 c.c.; albumin present during fever and at times hyaline casts; both absent during afebrile periods; bile present during pneumonia.

Blood: March 12, incoagulable nitrogen, 62.8 mg. per 100 c.c.; urea nitrogen, 17.5 mg. per 100 c.c.; April 22, incoagulable nitrogen, 36.4 mg. per 100 c.c.; urea nitrogen, 8.4 mg. per 100 c.c.; uric acid, 5.2 mg. per 100 c.c.

TABLE 6.—DATA OF RENAL FUNCTION IN CASE 6

April 21, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	75	1.018	0.74	0.55	0.71	0.53
10 to 12 a. m.	90	1.017	0.88	0.8	0.75	0.68
12 to 2 p. m.	190	1.006	0.18	0.34	0.29	0.55
2 to 4 p. m.	50	1.017	0.62	0.31	0.71	0.35
4 to 6 p. m.	190	1.011	0.32	0.61	0.52	0.99
6 to 8 p. m,	110	1.012	0.39	0.43	0.4	0.44
Total day	705	.....	0.43	3.04	....	3.54
8 p. m. to 8 a. m.	435	1.016	0.56	2.44	0.52	2.26
Total 24 hours	1,140	.....	0.48	5.48	....	5.8

Phthalein elimination, per cent., first hour, 30; second hour, 10; two-hour total, 40.

Summary: Slight nocturnal polyuria; slightly impaired dye excretion; water and salt retention.

CASE 7.—(163362.) Isidore K., aged 12½. Previous history, tonsillitis one year before.

Present illness began April 15 with chills, pains in chest and fever; temperature became normal May 6, three days after admission; physical signs of pleurisy with effusion. Blood pressure, systolic 105, diastolic 50.

Urine: Twenty-four-hour specimens, specific gravity, 1.015 to 1.025; albumin, a faint trace found twice only; no casts.

Blood: May 12, incoagulable nitrogen, 37 mg. per 100 c.c.; urea nitrogen, 23 mg. per 100 c.c.

TABLE 7.—DATA OF RENAL FUNCTION IN CASE 7

May 10, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	220	1.017	0.46	1.01	0.82	1.8
10 to 12 a. m.	85	1.023	0.48	0.41	1.33	1.12
12 to 2 p. m.	60	1.018	0.53	0.32	0.96	0.58
2 to 4 p. m.	100	1.018	0.42	0.42	1.02	1.02
4 to 6 p. m.	180	1.011	0.2	0.36	0.69	1.24
6 to 8 p. m.	170	1.017	0.23	0.39	1.4	2.38
Total day	815	.....	0.35	2.91	....	8.14
8 p. m. to 8 a. m.	250	1.021	0.59	1.49	1.3	3.33
Total 24 hours	1,065	.....	0.41	4.4	....	11.47

At 12, failed to take soup, green vegetable and half the bread.

Phthalein elimination, per cent., first hour, 18; second hour, 16; two-hour total, 34.

Summary: There is a tendency toward fixation in the salt excretion. The total salt output is low. Dye excretion is moderately impaired.

CASE 8.—(163002.) Hyman A., aged 24. Past history negative.

Present illness, typhoid with fever lasting until May 5.

Blood pressure, systolic 125, diastolic 60.

Urine: Twenty-four-hour specimens, quantity 850 to 2,000 c.c.; specific gravity, 1.010 to 1.022; albumin present from May 1 to 9 only; no casts at any time.

Blood: May 11, incoagulable nitrogen, 45.7 mg. per 100 c.c.; urea nitrogen, 35 mg. per 100 c.c.

Phthalein elimination, May 11, per cent., first hour, 12; second hour, 15; two-hour total, 27.

TABLE 8a.—Data of Renal Function in Case 8

May 14, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	100	1.018	0.51	0.51	1.01	1.01
10 to 12 a. m.	85	1.018	0.61	0.52	1.02	0.87
12 to 2 p. m.	70	1.023	0.62	0.43	1.29	0.9
2 to 4 p. m.	100	1.024	0.75	0.75	1.13	1.13
4 to 6 p. m.	150	1.016	0.35	0.55	0.95	1.42
6 to 8 p. m.	230	1.010	0.19	0.44	0.53	1.2
Total day	735	.....	0.43	3.2	....	6.53
8 p. m. to 8 a. m.	420	1.017	0.51	2.14	1.2	5.04
Total 24 hours	1,155	.....	0.46	5.34	....	11.57

Summary: Slight nocturnal polyuria; slight water and salt retention; dye excretion moderately impaired.

This patient (Case 8) was seen again Dec. 25, 1916. He had been well in the interval. The urine was collected at two-hour intervals. Food and fluids were not limited. Meals were taken at 8, 12 and 5, and no fluid was taken except at meals.

Urine: Albumin, none; microscopically negative. Table 8b shows the other data:

TABLE 8b.—Data of Renal Function in Case 8

Dec. 25, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	70	1.035	0.67	0.47	....	....
10 to 12 a. m.	135	1.029	1.38	1.86	....	....
12 to 2 p. m.	140	1.028	1.48	2.06	....	....
2 to 4 p. m.	175	1.026	1.62	2.83	....	....
4 to 6 p. m.	125	1.030	1.44	1.8	....	....
6 to 8 p. m.	120	1.030	1.22	1.46	....	....
Total day	765	.....	....	10.48	1.66	12.7
8 p. m. to 8 a. m.	440	1.030	1.31	5.76	1.86	8.2
Total 24 hours	1,205	.....	....	16.24	....	20.9

Phthalein elimination, December 26, per cent., first hour, 40; second hour, 10; two-hour total, 50.

Summary: More than seven months after his acute illness the patient still shows a slight nocturnal polyuria and slightly impaired dye excretion.

It is unfortunate that the diet in this determination could not be better controlled. In spite of this, the results indicate that kidney function is not yet entirely normal.

Case 9.—(162806.) Abraham B., aged 25. Previous history, had pneumonia as a young boy.

Present illness, typhoid fever; temperature normal after May 4. Blood pressure, April 19, systolic 110, diastolic 70. Blood examination, April 14, hemoglobin, 110 per cent.; erythrocytes, 5,760,000.

Urine: Twenty-four-hour specimens, quantity, 600 to 1,600 c.c.; specific gravity, 1.012 to 1.022; albumin at times in a very faint trace; microscopically negative.

Blood: May 11, incoagulable nitrogen, 40 mg. per 100 c.c.; urea nitrogen, 11.2 mg. per 100 c.c.

TABLE 9.—Data of Renal Function in Case 9

May 14, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	220	1.016	0.94	2.07	0.72	1.58
10 to 12 a. m.	135	1.017	0.73	0.99	0.65	0.88
12 to 2 p. m.	110	1.019	1.03	1.13	0.8	0.88
2 to 4 p. m.	150	1.017	0.78	1.17	0.8	1.2
4 to 6 p. m.	230	1.011	0.43	0.99	0.41	0.94
6 to 8 p. m.	185	1.011	0.34	0.63	0.51	0.94
Total day	1,030	.....	0.68	6.98	....	6.42
8 p. m. to 8 a. m.	440	1.017	0.46	2.02	0.44	1.93
Total 24 hours	1,470	.....	....	9.00	....	8.35

Phthalein elimination, May 11, per cent., first hour, 10; second hour, 17; two-hour total, 27.

Summary: Slight nocturnal polyuria; moderately impaired dye excretion.

Case 10.—(161140.) Joseph G., aged 26. No previous illness. In the hospital from Jan. 18 to 24, 1916, with temperature up to 101.4 F., and a papular rash on the trunk. The Widal reaction was negative.

Urine: Specific gravity, 1.018 to 1.025; an occasional granular cast found in the first specimen after admission only.

Readmitted February 2 with a typical typhoid fever. Temperature normal after February 16.

Urine: Single specimens examined daily. Specific gravity 1.012 to 1.026; albumin, usually none; at times a faint trace; on only one examination were hyaline casts found.

Blood pressure, February 4, systolic 95, diastolic 55.

February 3, hemoglobin 65 per cent.; erythrocytes 3,264,000.

March 4, incoagulable nitrogen 59 mg. per 100 c.c. blood; urea nitrogen 18 mg. per 100 c.c. blood.

TABLE 10.—Data of Renal Function in Case 10

March 3, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	230	1.012	0.82	1.89	0.59	1.36
10 to 12 a. m.	235	1.012	0.82	1.93	0.45	1.05
12 to 2 p. m.	200	1.005	0.35	0.7	0.23	0.46
2 to 4 p. m.	225	1.007	0.43	0.97	0.24	0.54
4 to 6 p. m.	220	1.010	0.57	1.25	0.45	0.99
6 to 8 p. m.	100	1.021	0.97	0.97	0.87	0.87
Total day	1,210	.....	0.63	7.71	....	5.27
8 p. m. to 8 a. m.	580	1.016	0.82	4.76	0.66	3.83
Total 24 hours	1,790	.....	0.69	12.47	....	9.1

Phthalein elimination, March 4, per cent., first hour 33; second hour 23; two-hour total 56.

Summary: Definite polyuria throughout the test; unusually large salt output. There is a tendency to fixation in the amount of the two-hour urine. Almost normal dye excretion.

Case 11.—(163259.) Rose L., aged 33. Previous history negative.

Present illness, typhus fever. The temperature reached normal May 6. Blood pressure, systolic 100, diastolic 70.

Urine: Twenty-four-hour quantity about 1,000 c.c.; specific gravity 1.010 to 1.020; albumin at times in faint trace; no casts.

TABLE 11.—Data of Renal Function in Case 11

May 9, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	90	1.015	0.43	0.39	0.85	0.77
10 to 12 a. m.	70	1.016	0.47	0.33	0.46	0.32
12 to 2 p. m.	350	1.017	0.12	0.42	0.3	1.05
2 to 4 p. m.	150	1.015	0.25	0.38	0.59	0.89
4 to 6 p. m.	130	1.015	0.26	0.34	0.72	0.94
6 to 8 p. m.	350	1.006	0.13	0.46	0.7	2.45
Total day	1,140	.....	0.2	2.32	....	6.42
8 p. m. to 8 a. m.	460	1.017	0.28	1.29	0.75	3.45
Total 24 hours	1,600	.....	....	3.61	....	9.87

Phthalein elimination May 10, per cent., first hour 19; second hour 12; two-hour total 31.

Summary: There is slight polyuria during the day as well as at night. Salt output and concentration are both unusually low. Dye excretion is moderately impaired.

Case 12.—(163670.) Abraham C., aged 14. Previous history, measles and pertussis in early childhood.

Present illness, tertian malaria lasting two weeks in all; no fever after May 8.

Blood: May 16, hemoglobin 60 per cent., erythrocytes 3,700,000.

May 22, incoagulable nitrogen 46 mg. per 100 c.c.; urea nitrogen 32 mg. per 100 c.c.

TABLE 12.—Data of Renal Function in Case 12

May 24, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	35	1.023	0.18	0.06	1.52	0.53
10 to 12 m.	55	1.019	0.46	0.25	1.04	0.57
12 to 2 p. m.	75	1.022	0.76	0.57	0.45	0.34
2 to 4 p. m.	90	1.023	0.49	0.44	1.09	0.98
4 to 6 p. m.	75	1.025	0.47	0.39	1.39	1.04
6 to 8 p. m.	40	1.032	0.27	0.11	1.7	0.68
Total day	370	.....	0.48	1.78	....	4.14
8 p. m. to 8 a. m.	105	1.022	0.36	0.38	1.03	1.08
Total 24 hours	475	.....	0.45	2.16	....	5.22

Phthalein elimination, per cent., first hour 48; second hour 20; two-hour total 68.

Summary: Decided retention of water and salt; dye excretion normal.

Comment: During the malarial paroxysm, salt excretion has been found slightly increased, decreased after the fever has begun to decline and increased again immediately after the paroxysm (von Moraczewski: Virchows Arch. f. path. Anat., 1899, **155,** 11). The patient, six days after fever, shows decreased salt excretion. There is no sign of a nephritis, although many observers have reported that it occurs frequently after malaria.

Case 13.—(163331.) Fanny D., aged 15. Past history, repeated attacks of tonsillitis.

Present illness, for three or four weeks, fleeting pains in the joints; right knee and right wrist slightly swollen and a little tender to pressure since the end of April. These symptoms persisted until May 12. The temperature was never above 100 F.

Urine: Single specimens showed albumin, a faint trace usually present; in one of thirteen specimens many granular casts were found.

Blood pressure, systolic 80, diastolic 60.

Blood: May 10, incoagulable nitrogen 42.4 mg. per 100 c.c.; urea nitrogen 9.8 mg. per 100 c.c.

Phthalein elimination, per cent., first hour 13; second hour 33; two-hour total 46.

Summary: The examination was made during the existence of slight fever. The results of the test diet are normal. The salt output as a whole is rather low. Dye excretion is slightly impaired.

Case 14.—(162439.) Sophie B., aged 34. Past history, married eleven years; five normal pregnancies; no infectious diseases.

Present illness, grippe and tonsillitis beginning February 25. About March 10, legs began to swell. The quantity of urine decreased after that.

Urine: Twenty-Four Hour Specimens:

Specific Gravity	Albumin	Microscopic	Quantity, c.c.
March 31..... 1.020	Very faint trace	Very few hyaline casts	1,200
April 3..... 1.020	Very faint trace	No casts	1,600
April 9..... 1.020	None	No casts	1,200

Physical examination, March 30, showed edema of eyelids and of legs, which had disappeared before the test diet was given.

Blood pressure: April 4, systolic 140, diastolic 100.

Blood: April 2, incoagulable nitrogen 47 mg. per 100 c.c.; urea nitrogen 12.6 mg. per 100 c.c.

TABLE 13.—Data of Renal Function in Case 14

April 5, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	85	1.012	0.48	0.41	0.74	0.63
12 to 12 a. m.	235	1.007	0.48	1.13	0.35	0.82
12 to 2 p. m.	500	1.006	0.44	2.2	0.29	1.45
2 to 4 p. m.	85	1.015	0.71	0.6	0.81	0.69
4 to 6 p. m.	150	1.013	0.54	0.81	0.58	0.87
6 to 8 p. m.	130	1.013	0.28	0.36	0.66	0.86
Total day	1,185	.....	0.46	5.51	....	5.32
8 p. m. to 8 a. m.	250	1.024	0.53	1.33	1.36	3.4
Total 24 hours	1,435	.....	0.48	6.84	....	8.72

Phthalein elimination April 4, per cent., first hour 18; second hour 25; two-hour total 43. March 31, first hour 30; second hour 30; two-hour total 60.

Summary: The result of the test diet is normal. Dye excretion is slightly impaired.

Comment: There is here a definite clinical nephritis following acute tonsillitis and rheumatism. The dye test shows slight impairment. Indeed, by functional tests these kidneys are more nearly normal than those of many of our patients who had clinically only a febrile albuminuria.

Case 15.—(160926b.) Sidney R., aged 19. Past history, negative.

Present illness, *Staphylococcus aureus* meningitis. Three injections of antimeningococcus serum were given, the last on Jan. 26, 1916. Temperature range up to 105 F., reached normal March 5.

Urine: Repeated examinations were made of single specimens; specific gravity 1.016 to 1.035. During fever, albuminuria ++; many hyaline and granular casts and a few red blood cells. After February 25, albumin and casts no longer found.

TABLE 14a.—Data of Renal Function in Case 15

March 29, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	180	1.015	0.68	1.22	0.46	0.59
10 to 12 a. m.	145	1.015	0.94	1.36	0.54	0.78
12 to 2 p. m.	230	1.011	0.53	1.22	0.25	0.57
2 to 4 p. m.	220	1.011	0.57	1.25	0.26	0.57
4 to 6 p. m.	220	1.012	0.77	1.69	0.27	0.59
6 to 8 p. m.	220	1.009	0.48	1.06	0.32	0.7
Total day	1,215	.....	0.64	7.8	....	3.8
8 p. m. to 8 a. m.	560	1.012	0.63	3.53	0.43	2.41
Total 24 hours	1,775	.....	0.69	11.33	....	6.21

Phthalein elimination, March 27, per cent., first hour 45; second hour 25; two-hour total 70.

Summary: This patient shows slight fixation of the specific gravity and the quantity of the single specimens; polyuria both during the day and night periods, with low concentration of nitrogen at night. The salt excretion is increased. In spite of the normal dye excretion the whole impression is one of decided functional impairment.

This patient (Case 15) was seen at Montefiore Home and Hospital about a year after the first observations were made. His meningitis had left him paraplegic, but otherwise well. The following examinations were made:

Urine: Repeated examinations were made of the twenty-four hour collection; specific gravity 1.018; quantity, about 1,000 c.c. on house diet; casts and albumin were absent.

Feb. 24, 1817, phthalein elimination, per cent., first hour 8; second hour 20; two-hour total 28.

TABLE 14b.—Data on Renal Test Diet

April 3, 1917	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
7 to 9 a. m.	140	1.0205	....	....	....	....
9 to 11 a. m.	200	1.020	....	....	....	....
11 to 1 p. m.	175	1.0165	....	....	....	....
1 to 3 p. m.	140	1.015	....	....	....	....
3 to 5 p. m.	130	1.016	....	....	....	....
5 to 7 p. m.	120	1.017	....	....	....	....
Total day	905	.....	0.71	6.5	0.8	7.0
7 p. m. to 7 a. m.	455	1.020	0.78	3.5	0.8	3.6
Total 24 hours	1,360	.....	....	10.0	....	10.9

Mosenthal meals at 7, 11 and 4.

Summary: The changes during the year that has elapsed since the last examination are: the specific gravity shows the same amount of fixation but at a higher level; the total quantity is less; nocturnal polyuria is less marked. Phthalein excretion is now decidedly impaired.

TABLE 15.—SUMMARY

Case No.	Diagnosis	Days after Fever	Amount of Urine Excreted, C.c.		Specific Gravity*		Sodium Chlorid Excretion in Urine			Phthalein Excretion in 24 Hrs., per Cent.	Age of Patient	Previous History of Infectious Diseases or Nephritis	Urine. Clinical Diagnosis of Renal Lesion
							Percentage		Gm. in 24 Hrs.				
			Total in 24 Hrs.	Night Specimen	Range in 24 Hrs.	Night Specimen	Range for 24 Hrs.	Night Urine					
1	Acute lobar pneumonia	5	940	(415)†	19–31	19	0.62–1.11	0.62	7.7	(44.0)	30	.....	Febrile albuminuria
2	Acute lobar pneumonia	6	1,040	375	7–24	24	0.25–0.78	0.78	5.4	**38.0**	14	.....	Febrile albuminuria
3	Acute lobar pneumonia	8	1,630	(510)	8–17	(17)	0.25–0.74	0.74	8.0	88.0	18	.....	Slight febrile albuminuria
4	Acute lobar pneumonia	8	1,100	200	12–28	28	0.55–1.08	0.78	8.0	**39.5**	14	Scarlet fever	Febrile albuminuria
5	Acute lobar pneumonia	8	1,425	**640**†	(9–15)	**13**	0.33–0.64	0.33	5.5	(55.0)	22	Scarlet fever	Chronic nephritis?
6	Acute lobar pneumonia	11	1,140	(435)	6–18	(16)	0.18–0.88	0.56	5.5	(40.0)	32	Typhoid fever	Febrile albuminuria
7	Acute pleurisy with effusion	3	1,065	250	11–23	21	0.20–0.59	0.59	4.4	**34.0**	13	Tonsillitis	Slight febrile albuminuria
8a	Typhoid fever.....	8	1,155	(420)	10–24	(17)	0.59–0.75	0.51	5.3	**27.0**	24	.....	Slight febrile albuminuria
8b	Typhoid fever.....	230	1,205	(440)	26–35	30	0.67–1.62	1.31	16.2	(50.0)	24	.....	Negative
9	Typhoid fever.....	9	1,470	(440)	(11–19)	(17)	0.34–1.03	0.46	9.0	**27.0**	25	Pneumonia	Negative
10	Typhoid fever.....	15	1,790	(580)	5–21	(16)	0.35–0.97	0.82	12.5	(56.0)	26	.....	Slight febrile albuminuria
11	Typhus.....	3	1,600	(460)	6–17	(17)	0.12–0.47	0.28	3.6	**31.0**	33	.....	Negative
12	Malaria.....	5	475	105	19–32	22	0.18–0.76	0.36	2.2	68.0	14	Measles; pertussis	Slight febrile albuminuria
13	Subacute rheumatism	0‡	1,480	260	6–18	18	0.12–0.75	0.60	5.4	(46.0)	15	Tonsillitis	Febrile albuminuria
14	Tonsillitis; grippe	35	1,435	250	6–24	24	0.28–0.71	0.53	6.8	60.0 (43.0)	34	.....	Chronic nephritis
15a	Staphylococcus meningitis	23	1,775	(560)	(9–15)	**12**	0.53–0.94	0.63	11.3	70.0	19	.....	Chronic nephritis
15b	Staphylococcus meningitis	390	1,365	(455)	(15–21)	20	.....	0.78	10.0	**28.0**	20	.....	Chronic nephritis

* The figures mean above 1.000.
† Figures in parentheses = slight impairment; figures in heavy faced type = moderate impairment.
‡ Temperature constantly below 100 F.

Comment: The picture in this patient is in striking contrast to some of the patients with febrile albuminuria. In a number of these the impaired dye excretion was the only sign of kidney damage. Here, however, we have normal dye excretion in a patient who shows unmistakable renal disturbance. Ordinary methods of examination failed to reveal the undoubted chronic nephritis. Examination after the lapse of one year shows moderately impaired dye excretion, with persistence of the impairment in renal function as shown by the test diet. The damage to the kidneys has evidently grown worse.

Thanks are extended to Dr. Alfred Meyer and Dr. Morris Manges for the opportunity, so readily offered, of studying patients in their wards, and to Dr. Lester J. Unger, former house physician, for his valuable and efficient aid in organizing the work in the wards.

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HEART BLOCK ASSOCIATED WITH HIGH BLOOD PRESSURE *

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The following two cases present several instructive phases of cardiovascular disturbance which will be discussed in detail following the case histories.

REPORT OF CASES

CASE 1.—Mrs. G., aged 60; white; housework; born in Ireland; admitted Sept. 28, 1913; discharged Nov. 8, 1913. The patient was admitted with the diagnosis of acute appendicitis. Appendectomy was performed a few hours after admission to the ward and the appendiceal region drained. Recovery was slow and when the patient was discharged there was a persistent, discharging sinus. While in the surgical ward note was made, "heart beats with a very slow rhythm." The patient was discharged from the surgical service Nov. 8, 1913, and readmitted to the medical service Dec. 30, 1913, on account of dizziness, headache and faintness. She had complained of the buzzing in the head for the previous three months with headaches and dizziness, had had frequent dizzy spells, and on two occasions in the previous month she nearly fell to the floor owing to dizziness, but had never lost consciousness. She had had scanty urination with no pain or burning, occasional throbbing in the head, much shortness of breath, palpitation of the heart and slight swelling of the feet but no cough, no vomiting, some nausea and belching of gas, some general abdominal pain. The bowels were constipated. The patient had never fainted.

Examination of the heart showed a slight enlargement down and to the left. The aortic second sound was accentuated; there was a soft blowing systolic murmur at the apex.

The urine excreted while in the hospital varied between 700 and 900 c.c. in the twenty-four hours. The specific gravity in numerous examinations was always high. Traces of albumin and hyaline casts were regularly found. Phenolsulphonephthalein excretion the first hour was 10 per cent., second hour, 7 per cent. The temperature was always normal; the pulse rate varied between 32 and 68 per minute. The blood pressure estimations were as follows:

12/30	270 - 150?	Pulse rate about 40.
1/1	230 - ?	
1/4	230 - 90	
1/7	204 - 118	
1/10	194 - 78	
1/12	182 - 76	

Mrs. G. was seen from time to time after her discharge. She was last visited in November, 1916. At that time the pulse rate was extremely slow (36) and it had been continuously since leaving the hospital. On account of an ignorant prejudice of her husband against mechanical medical instruments, permission had been refused for any type of examination, and I have been unable to take the pressure or make tracings. The same essential conditions, however, were apparently present as when in the hospital. Cardiac compensation was good, but there

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had evidently developed a certain amount of cerebral softening, as the mentality was decidedly feeble.

Case 2.—Mrs. W., aged 65; white; occupation, housewife; admitted Sept. 26, 1913; discharged Nov. 7, 1913.

This patient was seen in the medical dispensary, where, in the course of the routine examination, it was found that she had a blood pressure of 270 systolic, 140 diastolic. On account of the cardiovascular condition she was referred to the ward where the following notes were made:

"Shortness of breath on exertion; weakness; cardiac palpitation. Began to have shortness of breath, weakness, and to feel the heart beat about the end of May; cannot do any work or exercise; walking, going upstairs and all such efforts bring about these symptoms; the patient also gets, at times, shooting pains on the left side of the thorax which radiate to the precordia, and to the left shoulder and down the left arm. The symptoms have gradually been getting worse.

"The patient has had general good health, except for the latter part of her life. Had measles, whooping cough, mumps and diphtheria in childhood; was then in good health until four years prior to admission, when she had nervous prostration lasting about two months; began to feel cardiac palpitations after this. These were soon followed by inflammatory (?) rheumatism, polyarticular, lasting about six weeks; the pain reappearing at intervals up to the present. She has had frequent attacks of sore throat, though of mild characteer.

"The patient's mother died of stroke of paralysis at 53; father died with considerable anasarca at 63; had nine brothers and sisters, eight of whom are dead.

"Married forty-five years; did her own housework till husband's death thirty years prior; after that did outside general housework. Had three children; no miscarriages. Denied the use of alcohol and tobacco.

"Physical Examination.—The patient is an old female, well built and preserved. The physical findings are negative except for those of the cardiovascular system.

"Heart: Apex beat; visible in fifth interspace one-half inch to left of the midclavicular line, very irregular and slow in rhythm, and the beat is moderately strong; normal area of dulness; sounds weaker than normal and irregular; no valvular murmurs heard; peripheral arteries show slight thickening; ophthalmoscopic examination showed slight sclerosis of retinal vessels.

"September 28: No apparent change since admittance. Feels comfortable while in bed without exertion. Pulse tracing shows heart block.

"October 1: Slightest exertion seems to stir up the heart to beat more rapidly. Has no difficulty while remaining still.

"October, 7: Blood pressure, 165-75; weight about the same.

"October 31: Nothing indicating extra systoles or blocked beats. Temperature, pulse and respiration normal. General condition good.

"November 7: Condition about the same as last note; no change found. Appears in good condition and has not felt uncomfortable for several weeks."

Laboratory Reports.—Blood: red blood count, 3,630,000; white blood count, 12,100; hemoglobin 62 per cent.; Wassermann, negative.

Urine: In twenty-seven examinations, traces of albumin were found at times, as well as occasional hyaline casts. Excretion varied between 500 and 1,800 c.c.; sp. gr., 1.010 to 1.032.

After four or five days in bed the pulse increased from an average of 48 to 60 beats per minute, to 80 to 100. The blood pressure while in bed during the latter part of the patient's stay in the ward was never over 165 systolic, 125 diastolic. According to the method of Stone her heart showed an overload of 47. The pulse work (Sahli) varied from 7.1 mm. Hg lying down to 14.96 mm. Hg while sitting up. During the interval following discharge from

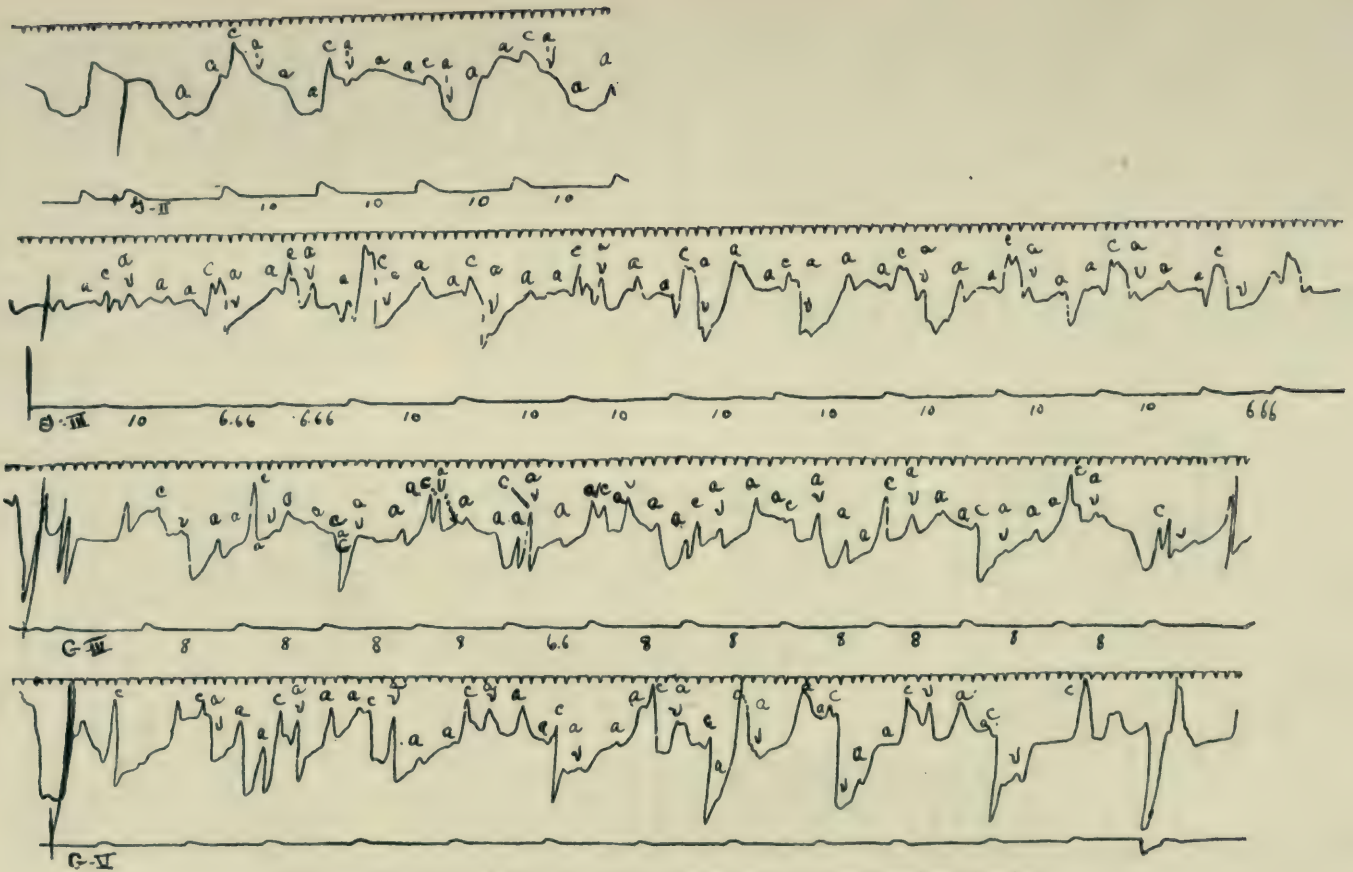


Fig. 1.—Tracings of Mrs. G., taken during stay in Presbyterian Hospital.

the hospital Mrs. W. was in fairly good condition. She was able to do a fair amount of housework without much discomfort. I saw her from time to time and noted that heart rate fell shortly after leaving the hospital and remained persistently low afterward. At my request she was readmitted to the hospital in October, 1916, for further observation. At that time the following notes were made:

"The patient has been suffering from shortness of breath for several years. She becomes very short of breath on slight exertion; walking across the room often forces her to sit down to rest. She has attacks of precordial pain which are brought on by slight exertion. The pain radiates to the shoulder and arm. She is unable to lie flat, but always sleeps propped up by several pillows. At times she has swelling of the ankles. She has had a cough for several years. Each morning she has a coughing spell lasting five or ten minutes. She is bothered very little the rest of the day by the cough. Phlegm accompanies the cough. She has no cardiac palpitation, but, on the contrary, she says at times her heart seems to beat hardly at all. The bowels are regular; appetite good; occasionally has attacks of nausea and vomiting just after eating; no trouble at urination; no nycturia. At times she has a little bearing down pain after urination.

"At the base of the lungs there are fine, moist râles. Heart sounds are clear but very slow and irregular. With the stethoscope on the point of maximum impulse the heart sounds do not correspond with the pulsation over the jugular vein, they being very much faster than the apical pulsations. All the beats heard at the apex come through to the radial. There is a soft systolic murmur over the mitral area. No murmur is heard at the aortic or pulmonary area; heart border—above, third rib; to the left, 1½ in. outside of midclavicular line; to the right, sternal line; aortic second sound accentuated; slight sclerosis of radials; blood pressure, 220-75.

"October, 12: Patient's general condition is good. She has no pain. She walks around the ward a little each day.

"October 17: Condition about the same. She complains of pain about the heart. Blood pressure, 230-65."

Laboratory Reports.—Urine in five examinations showed no casts; a very faint trace of albumin twice; sp. gr., between 1.019 and 1.029.

Blood: Hemoglobin, 60 per cent.; red blood count, 3,980,000; white blood count, 9,900.

The temperature was continuously normal; respirations varied between 24 and 16; the pulse rate was uniformly between 38 and 48, once or twice going over the latter figure.

GRAPHIC EVIDENCES OF HEART-BLOCK

The polygraphic tracings of Mrs. G. will first be discussed. G-II, taken on admission to the ward, shows a 3:1 block. As G-III shows more clearly than G-II the sequence of events, and as the two tracings illustrate the same condition, the former alone will be discussed. This tracing was taken preliminary to an injection of atropin. It can be noted in the tracing of the radial artery that each ventricular systole for the most part occurs two seconds after the preceding one. Occasionally, however, an impulse comes through from the auricle which causes a corresponding contraction of the ventricle. These ventricular systoles, when they occur, are 1.33 seconds apart and are due to the temporary change of a 3:1 to a 2:1 block. The jugular tracing shows,

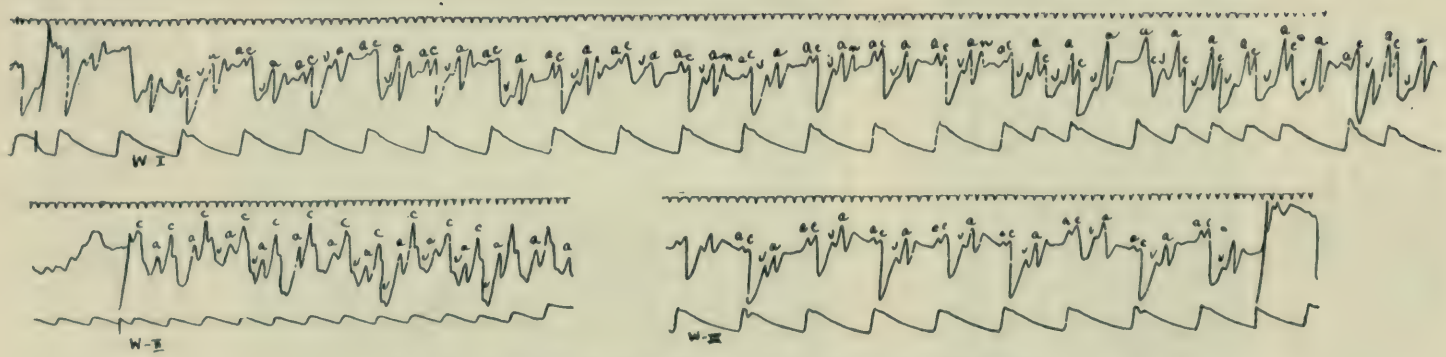


Fig. 2.—Tracings of Mrs. W., taken in Presbyterian Hospital.

except where the extra ventricular beats occur, a regularly recurring series of *a* waves which are 0.66 of a second apart. The first *a* wave is not followed by ventricular response; the second *a* wave is followed by the usual *c* and *v* waves; a third *a* wave occurs synchronously with the the *v* wave. The evidence that such synchronism takes place is based on the fact that the distance each *a* wave is from the next is equivalent to the distance from *a* to *v* to *a;* furthermore, the time interval between each ventricular response is two seconds, excepting where the additional beats appear, due to change in the rate of block to 2:1, when it is 1.33 seconds. If the rhythm were a 2:1 rhythm rather than a 3:1 rhythm, then the interval of this additional ventricular response would be exactly one second. Likewise, it would seem to be unlikely that a 2:1 rhythm is present, because the auricle would then contract twice at a rate of approximately 90 per minute, after which there would be a pause followed by another series of two beats. Such a condition is possible but improbable, and necessitates the assumption of a 2:3 sino-auricular block, as well. The auricles may contract irregularly when there is abnormal vagus irritability; for example, sinus arrhythmia, when extra systoles arise in the sinus or the auricle, when there is sino-auricular block and when there is auricular fibrillation; but none of these conditions is suggested in the tracing. Sinus arrhythmia, sinus or auricular extra systoles and auricular fibrillation can be ruled out at once, although a sino-auricular block might possibly be present; but as such a condition is rare, it seems fair to hold that the third auricular contraction occurs at the same time as the ventricular.

The next tracing, G-IV, illustrates a tracing taken ten minutes after the hypodermic injection of 0.2 mg. atropin sulphate. The same sequence of events takes place, except that the auricular, and consequently the ventricular, rate is more rapid as a result of the suppression of the inhibitory effect of the vagus by the atropin.

G-V is a tracing taken twenty minutes later. Again the same sequence of events occurs. In both the tracings taken after atropin was injected, there is no essential change in the character of the block, showing it to be organic rather than functional in type.

The graphic studies of Mrs. W. include not only polygrams, but also electrocardiograms. The tracing, W-I, taken in 1913, is presented as a long strip in order to show towards the end of the tracing a few contractions that arise as a result of impulses coming through without blocking in the bundle of His. Here the phlebogram shows a normal tracing. Elsewhere an additional *a* wave is shown which is followed by an extra wave (*n*) the genesis of which I have been unable to determine and which may be an artefact due to instrumental "fling." The tracing then shows a partial (2:1) block with occasional periods when

beats get through normally. It is interesting to note the differences in size of the arteriogram waves where there is block and where the block has disappeared. The waves are almost twice as large when the rate is slow as compared with the heart beats when twice as rapid, demonstrating that when all other factors are equal, the adjustment of levers

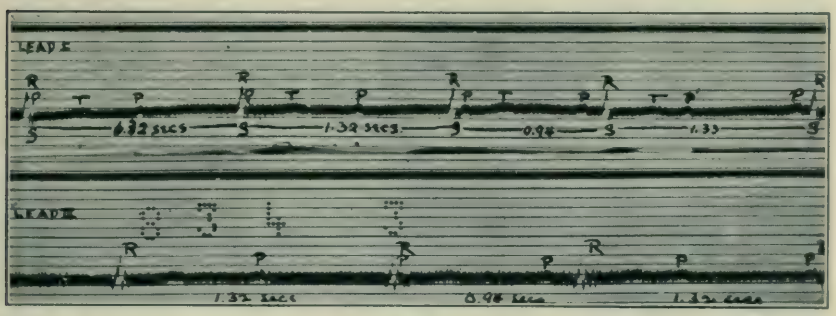


Fig. 3.—Electrocardiogram of Mrs. W., taken Sept. 14, 1916. Leads I and III.

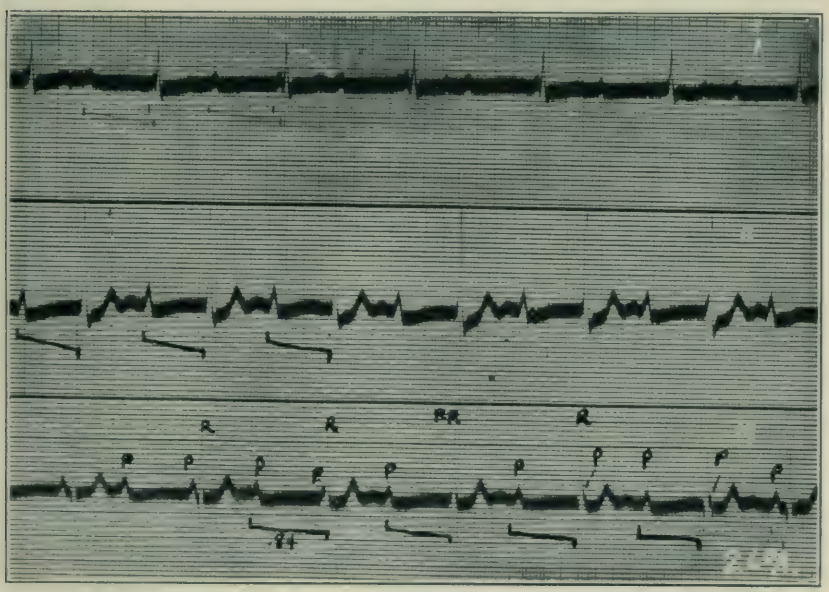


Fig. 4.—Electrocardiogram of Mrs. W., taken Oct. 10, 1916

being unchanged, a high pressure, presumably, causes large graphic arterial waves. Tracing W-III was taken two days after admission to the ward and following an injection of 0.3 mg. of atropin. There is no essential or minor change in the tracing as compared with the part of W-I that shows 2:1 block. Tracing W-II was taken two weeks

after rest in bed. Here a practically normal tracing is shown, except that there is possibly a slight prolongation of the a-c interval. The first electrocardiogram, Lead 1, taken September, 1916, shows partial heart block. The ventricular complex occurs every 1.32 seconds, the

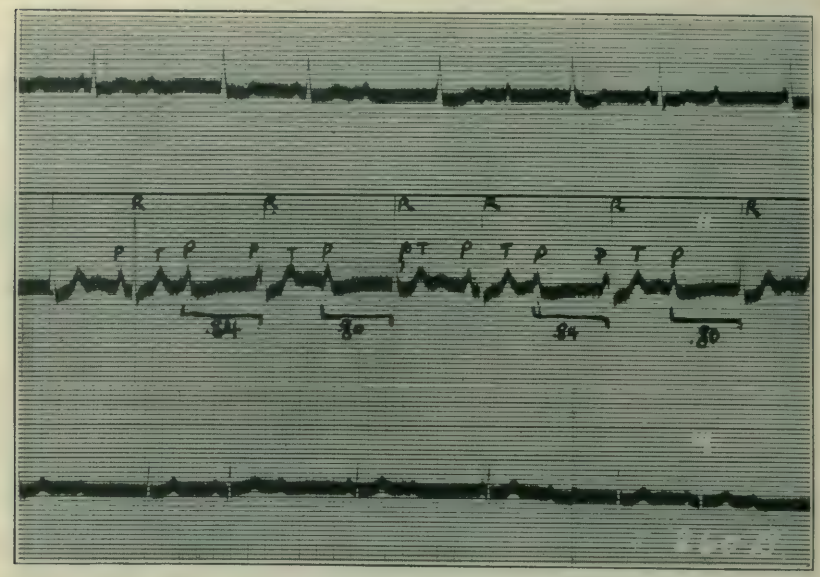


Fig 5.—Electrocardiogram of Mrs. W., taken Oct. 12, 1916.

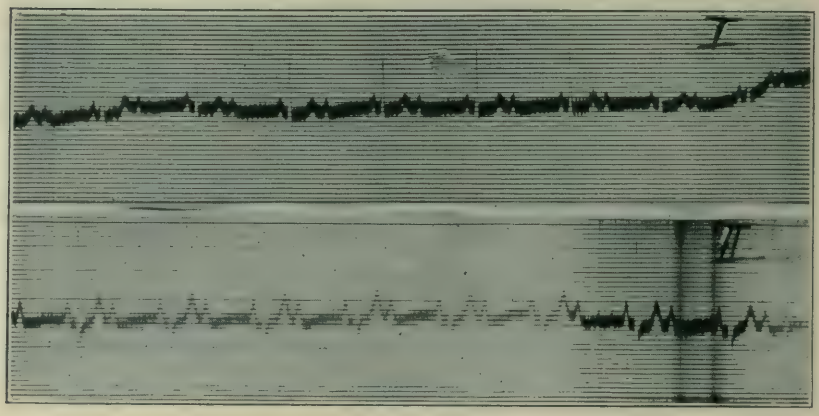


Fig. 6.—Electrocardiogram of Mrs. W., taken Oct. 23, 1916. Lead III not entirely clean and hence not reproduced.

auricular every 0.66 second, in the periods of 2 : 1 block. The P waves show a complex relationship to the R S T group, caused by the fact that the partial block varies at irregular intervals between a 2 : 1 and a 3 : 2 grade. The short cycles represent the 3 : 2 block, the longer cycles

the 2:1 block. The P-R intervals are greatly prolonged and vary according to the degree of refractility that exists at the moment in the junctional tissues. Tracings 260 A and B were taken one month later. Here the ventricular rate is 1.45 seconds, or approximately 42 per minute. Here again there is partial dissociation, with the block varying between a 2:1 and a 3:2 rhythm with a P-R interval that is 0.84 second long at times (see 260-B, Lead II). Tracings 264 and 267, taken thirteen and fifteen days later, respectively, show a clear 2:1 block with a normal P-R interval; 260-A shows a 2:1 rhythm, where every other P falls exactly or almost on the R of the preceding cycle. In Lead II the cycles are constant. In Lead III in the first cycle P is

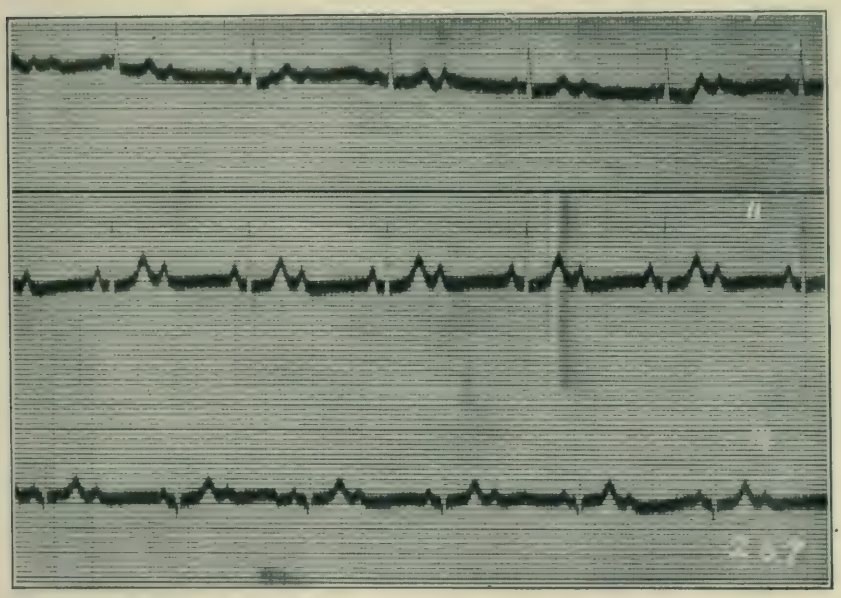


Fig. 7.—Electrocardiogram of Mrs. W., taken Oct. 25, 1916.

0.19 of a second from R, but with each cycle, gets nearer, then merges (note the higher R wave), then appears on the down stroke; conductivity improves gradually until the last cycle shows *no* block. In Lead I, the second P hovers about R, at first receding from it, then approaching, till in the last cycle it is merged.

From the evidence here presented the two patients unquestionably had heart block. The first showed but little change in the character of the block at any time. The several tracings taken of patient, Mrs. W., showed variations from a normal tracing to different degrees of partial block, at times associated with an extremely prolonged P-R interval.[1]

1. Thayer: The Archives Int. Med., 1916, **17,** 13.

BLOOD PRESSURE FINDINGS

The most interesting determination in these two cases was the extremely high systolic pressure. In both of them the pressure during the block and before rest in bed was higher than the Nicholson sphygmomanometer can register. In reviewing the literature[2] of heart block from 1904 to 1916, I was able to find cases of heart block associated with high systolic pressure reported by Bramwell (systolic pressure 235), Falconer (systolic pressure 230 during attacks), Gibbes and Dally (systolic pressure 240-Pachon), Gibson (pressure of 270), Gossage (pressure 200-220), Griffith and Kennedy (systolic pressure as high as 260), Grosh (pressure 225), Herrick (two cases, systolic pressure 240 and 200, respectively), Hoffman (two cases, pressure of 240 and 250, respectively), Hume (systolic pressure 230), Jellinek and Cooper (two cases with pressures over 200), Levine (systolic pressure 196), Purser and Davis (systolic pressure 214 during attack, 180 in the interval), Schwarzmann (systolic pressure 235), Souques and Routier (two cases, systolic pressure 250 and 220, respectively). In none of these cases did the systolic pressure approach closely the pressure in the two cases detailed above. The pressure of these two patients was first taken after they had been doing a certain amount of work. After rest in bed the pressure of both fell very materially; in Mrs. G's case about 100 mm. Hg; in Mrs. W's case somewhat more. When the block disappeared in the latter patient's case after rest in bed, the systolic pressure never exceeded 155, though the diastolic pressure remained high. These figures of 155-125 probably represent the true pressure without relation to the block, as they were found only when the block disappeared. Although the block returned shortly after the first stay of Mrs. W. in the ward, nevertheless, the possible dangers of the extremely high pressure having been fully explained to her, she so altered her manner of living that she took no violent, sudden or continuous exertion of any kind, and made no severe demand on the heart. Her pressure, even with the block present under these circumstances, never attained the heights reached on the first examination, which was made after resting a short time from a long walk.

Both of these patients were obviously cases of cardiosclerosis with associated fibrotic changes in the bundle of His. The first patient had apparently comparatively slight peripheral sclerosis, if we may judge from the low diastolic pressure. The second apparently had considerable peripheral resistance, as her diastolic pressure remained consistently high. In this patient the sclerotic changes evidently are progressing steadily, as the block no longer disappears after rest in bed.

2. References to the literature will be found alphabetically arranged at the end of the article.

Probably one of the most instructive points demonstrated in the study of these two cases is the relationship of extremely high blood pressure to the cardiac strength and complete filling of the ventricle. The systolic pressure represents the strength of the heart beat, and is dependent largely on the diastolic filling of the ventricles and the completeness of systolic emptying. In these two patients the pressure was raised very markedly; there were the factors of complete filling of the ventricle as a result of the very slow ventricular rate which Henderson believes increases the amplitude of the systolic discharge, and also the fact that with each beat the ventricle was filled by the extra auricular beats with more blood than it would receive under ordinary circumstances, though Wiggers[3] does not believe that auricular systoles aid materially in filling the ventricle. Furthermore, a ventricle in low tone has a greater systolic output than one of high tone, provided it is not fatigued and dilated, but is able to expel all the blood — to empty itself completely with each systole.

The complete filling of the ventricle had apparently a very distinct effect on the pressure, because on the one individual whose block disappeared, in spite of the cardiac hypertrophy, systolic pressure fell some 100 mm. Hg when the block was abolished. In other words, the very high systolic pressure apparently depended not so much on the strength of the heart muscle, but on the very complete filling of the ventricle with subsequent contraction on a large mass of blood. This has been shown by physiologic experiments; an increased systolic output causes a rise in systolic and diastolic pressure, provided the pulse rate and peripheral resistance remain constant. On a similar basis can be explained the extremely high pressures associated with aortic insufficiency. The left ventricle contains much more blood than normal, owing to the regurgitation of the blood backward into its chambers. As a result of this the ventricle is enabled to contract with the maximum amount of strength on a large amount of blood, resulting in a high systolic pressure. In both disorders, aortic regurgitation and heart block as here shown, there is, of course, the added factor of the cardiac hypertrophy, but in cardiac hypertrophy unassociated with these lesions, very high pressure is the exception, though relatively high values occur. It is by the forcing out of the larger volumes of blood with each ventricular contraction into the arterial tree that the pressure is raised so markedly, rather than by the ventricular hypertrophy per se. This latter condition is common where pure aortic obstruction exists, but the systolic pressure is usually only slightly elevated despite the hypertrophy, and the frequently associated arteriosclerotic changes. In

3. Wiggers: Circulation in Health and Disease. Lea and Febiger, Philadelphia and New York, 1915, p. 68.

the tracing W-1 the difference in the size of the pulse waves when the ventricle is not so completely filled, is graphically shown.

SUMMARY

Two cases of heart block with extremely high systolic pressure are recorded. Evidence is offered to show that this high pressure is dependent more on increased blood mass discharged by the left ventricle than on the associated cardiac hypertrophy and peripheral sclerosis.

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STUDIES IN THE VARIATIONS OF THE TONUS OF THE GASTRIC MUSCULATURE IN HEALTH AND DISEASE*

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The alterations in structure of any of the body organs, when produced by disease, are of greatest clinical importance when accompanied by disturbances in the function of the involved part. The function of the musculature of the stomach, that is, its motor function, is one of the most essential attributes of that organ; disturbances of this function characterize many of the earliest stages of gastric diseases. In this paper we have attempted to correlate the results of our studies on the variations of the functions of the gastric musculature in diseased conditions. Kymographic methods were utilized in their demonstration, as described by Cannon and Washburn[1] and by Carlson[2] and his associates, and studies of gastric hunger contractions and gastric tonus were carried on.

HISTORICAL

In 1877, von Pfungen[3] demonstrated, in the antrum of the stomach of animals, contractions occurring regularly three times a minute.

Morat,[4] in 1882, made use of a rubber balloon attached to the end of a stomach tube and recorded intragastric pressures. His tracings evidenced respiratory, cardiac and gastric elements.

In 1895, Moritz[5] obtained readings of intragastric pressure under various conditions. He utilized the method of an inflated balloon attached to a stomach tube, which he introduced into the stomach. The normal pressure within the healthy stomach of man varied between 2 and 16 cm. of water. He demonstrated a difference in pressure between the antral and fundic portions of the stomach, and made some observations on himself after the administration of such drugs as

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** This study was carried on under the tenure of a George Blumenthal, Jr., Fellowship in Pathology.

1. Cannon and Washburn: Am. Jour. Physiol., 1911-1912, **29,** 441.
2. Carlson, A. J.: Am. Jour. Physiol., 1912, **31,** 175 and 221; ibid., 1913, **32,** 245.
3. Von Pfungen: Centralbl. f. Physiol., 1877, p. 220.
4. Morat: Arch. de Lyon méd., 1882, p. 882.
5. Moritz: Ztschr. f. Biol., 1895, **24,** 313.

bicarbonate of soda and tartaric acid. He recognized, both in the fasting and in the digesting stomach, the occurrence of contractions which followed one another three to three and one-half times each minute, which contractions continued for periods of fifteen to ninety minutes, and which were separated by intervals of rest. The presence of food in the stomach inhibited these contractions. By means of double balloons he was able to demonstrate activity in the antrum, which was synchonous with a state of rest in the fundus.

Ducchessi[6] applied the same method in animal experiments and found that an increase of intragastric pressure caused the appearance of rhythmic contractions. He showed distinct differences between contractions of the cardiac, fundic and pyloric parts of the stomach and confirmed in animals the presence of the rhythmic contractions described by Moritz in man. He was of the opinion that the empty stomach remained in a state of rest, but that the introduction of food or of the inflated balloon gave rise to the typical contractions which he observed. Excision of the celiac plexus was followed by a change in the contraction wave. With the occurrence of pathologic lesions a depression of gastric tone was observed.

Sick,[7] in 1906, employed a complicated apparatus by means of which he was able to obtain records of intragastric pressures and stomach contractions, and specimens of stomach contents for chemical examination. Using the facts obtained from normal subjects as criteria, he made observations also in pathologic conditions.

Boldyreff,[8] in exhaustive studies on the alimentary canal, demonstrated waves of contraction originating in the stomach and sweeping downward throughout the entire extent of the alimentary canal. They bore some relation to the empty state of the stomach, disappearing with the ingestion of food and reappearing some time later.

In 1911, Cannon and Washburn,[1] in the course of investigations on the cause of hunger, demonstrated periods of gastric excitability evidenced by peristaltic waves, which occurred synchronously with sensations of hunger. The conditions necessary for the appearance of these contractions were a tonic state of the neuromusculature, plus some increase in the intragastric pressure. The point of origin of these contractions was not fixed. Most important of all, Cannon and Washburn[1] maintained that hunger contractions were evidences of healthy tone in a normal stomach.

About a year later, Carlson[2] was fortunate in finding a man with a gastric fistula which allowed of physiologic investigations. In this man

6. Ducchessi: Arch. ital. de biol., 1897, **27,** 61.
7. Sick: Arch. f. klin. Med., 1906-1907, **88,** 169.
8. Boldyreff: Zentralbl. f. Physiol., 1904, **18,** 489.

he was able to confirm all the statements of Cannon and Washburn.[1] He demonstrated in the kymographic tracings two types of contraction: one, a slow, periodic wave due to the normal tonal variations, which passed over the stomach three to four times a minute; second, a type of more powerful contractions, occurring in groups, lasting from fifteen

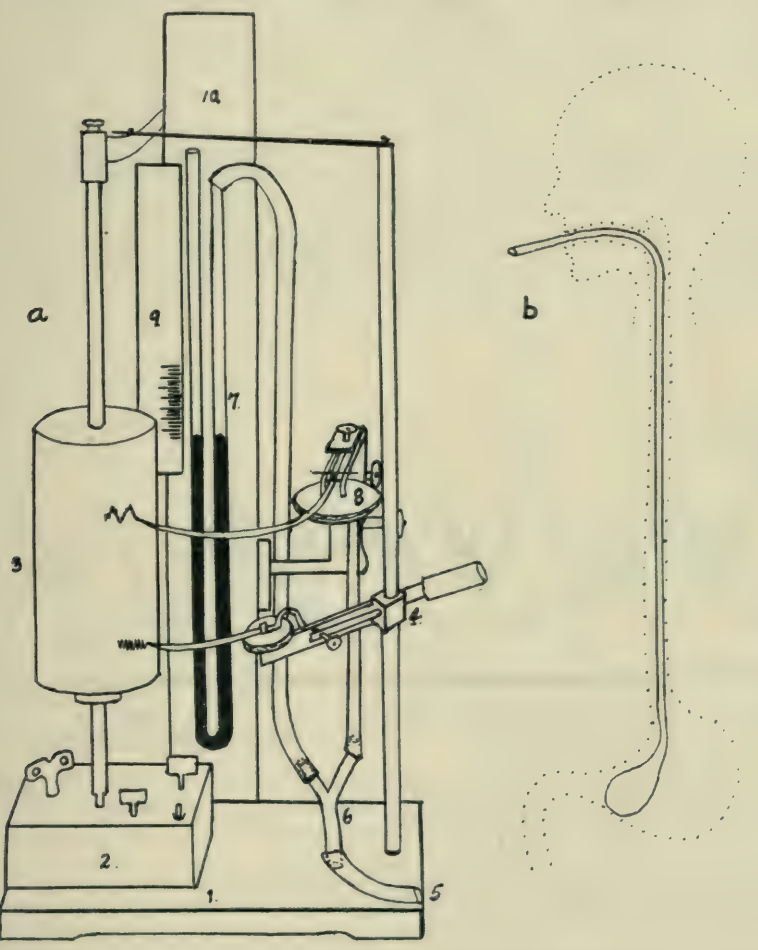


Fig. 1.—*a*, 1. Stand. 2. Clock work for revolving kymograph. 3. Kymographic drum. 4. Bracket supporting tambour and needle and connected with pneumograph about patient. 5. Tube connecting with balloon in patient's stomach and connecting with Y tube (6) to manometer (7) and tambour and needle (8). 9. Manometer scale. 10. Upright fixed to stand supporting apparatus, *b*, balloon and tube in stomach (diagrammatic).

to sixty or more minutes and separated by long periods of comparative inactivity. These last corresponded to the sensations of hunger and were easily inhibited by various causes, such as the act of swallowing or

the administration of various foods and drugs. The period of contractile activity was always accompanied by a period of slow gastric secretion.

We were enabled to apply this physiologic method in a series of pathologic cases in the hospital.[9] These cases included practically all the varieties of gastric diseases ordinarily encountered, such as gastric neuroses, gastric atony, vagotonia, secretory disturbances and organic lesions such as ulcer and carcinoma.

METHOD

A uniform technic was followed in all of these cases; an apparatus was used practically identical with that employed by Cannon and Washburn[1] and by Carlson.[2] The patient swallowed a collapsed toy balloon attached to the end of a narrow-caliber rubber tube. The free or proximal end of the latter was attached by a Y tube to both a mercury manometer and a tambour with its recording needle; the movements of the needle were in turn recorded on a slowly revolving drum. The respiratory element of the curve was controlled

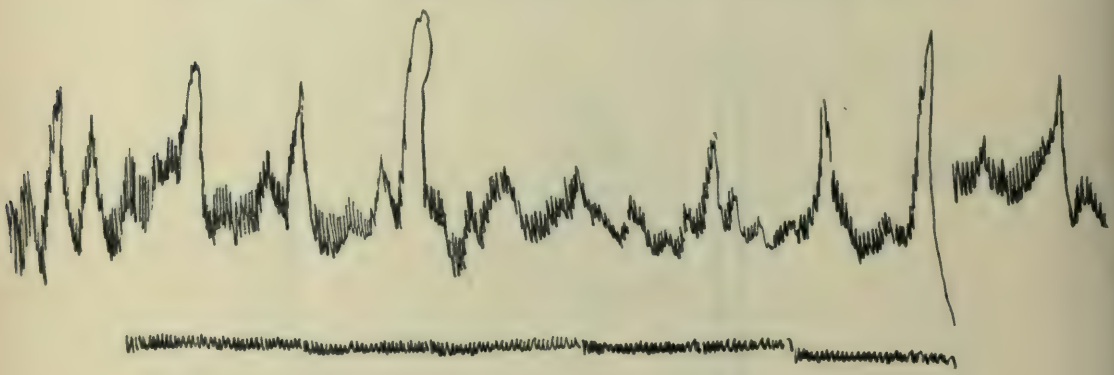


Fig. 2.—Kymograph tracings taken from normal individuals showing normal tonus and hunger contractions.

In this and the following figures the upper curve represents the gastric variations, the lower curve is a control obtained from a pneumograph fastened about the lower thorax and upper abdomen.

by a pneumograph fastened over the lower thorax and upper abdomen. Time was recorded manually in minutes. Observations were maintained for periods of from one-half hour to one hour and in cases where no contractions were observed in this time, the observation was repeated on a subsequent day. Extraneous influences, such as the presence of food, swallowed saliva, or other physical disturbances, were eliminated. In practically all instances the patients reposed quietly on the table, and frequently dropped off to sleep during the course of the observation. No record was accepted when the patient evidenced intolerance of the tube and balloon.

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9. We acknowledge our indebtedness to Drs. Brill, Libman, Manges and Meyer of the first and second medical services of the Mount Sinai Hospital, and to Dr. Aronson, chief of the gastro-enterologic department of the dispensary, for their courtesy in permitting us to make these observations on the patients under their care.

OBSERVATIONS

Gastric Neuroses.—These include those customarily seen in hospital ward or dispensary service. The records obtained from these patients did not vary particularly from those obtained from normal persons. That is, they evidenced normal tonal waves, recurring rhythmically and usually regularly, sometimes as slowly as once per minute, usually more rapidly, as two or three times per minute. The average tonal rise corresponded to about 5 mm. Hg. In the cases of neurosis the regular rhythm was sometimes disturbed by a varying degree of irregularity. The hunger contractions, which were always present in these organically sound stomachs, appeared singly or in groups. They were characterized by a steady rise of the lever, lasting over two or three respirations, until a pressure of 20 to 30 mm. Hg was registered, and following which there was a sudden drop to the base line. The rise of the lever

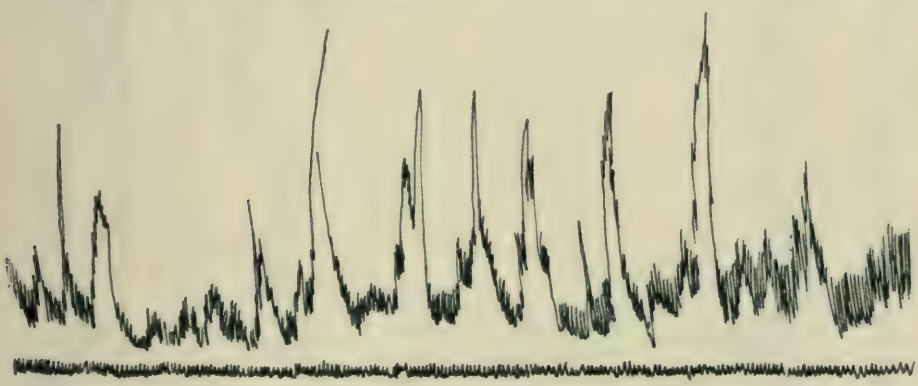


Fig. 3.—Tracing from a case of gastric neurosis, demonstrating good tone and continuous hunger contractions.

may be continuous, corresponding to a single powerful contraction, or may consist of several superimposed contractions. The fastigium is held for a fraction of a minute only. Occasionally, on the introduction of the balloon, no contractions appeared at first, but after a lapse of ten to twenty minutes the inhibitory influence of the foreign body passed away and tonal waves and hunger contractions made their appearance.

Vagotonia.—In a well marked case of vagotonia, hunger contractions predominated in the curve and demonstrated an extreme degree of excitability, the contractions following one another in rapid succession and without pause for comparatively long periods of time.

Functional Secretory Cases.—These include hyperacidities, subacidities and anacidities. These regularly show no disturbance in the motor function. Occasionally in marked instances of continuous hyper-

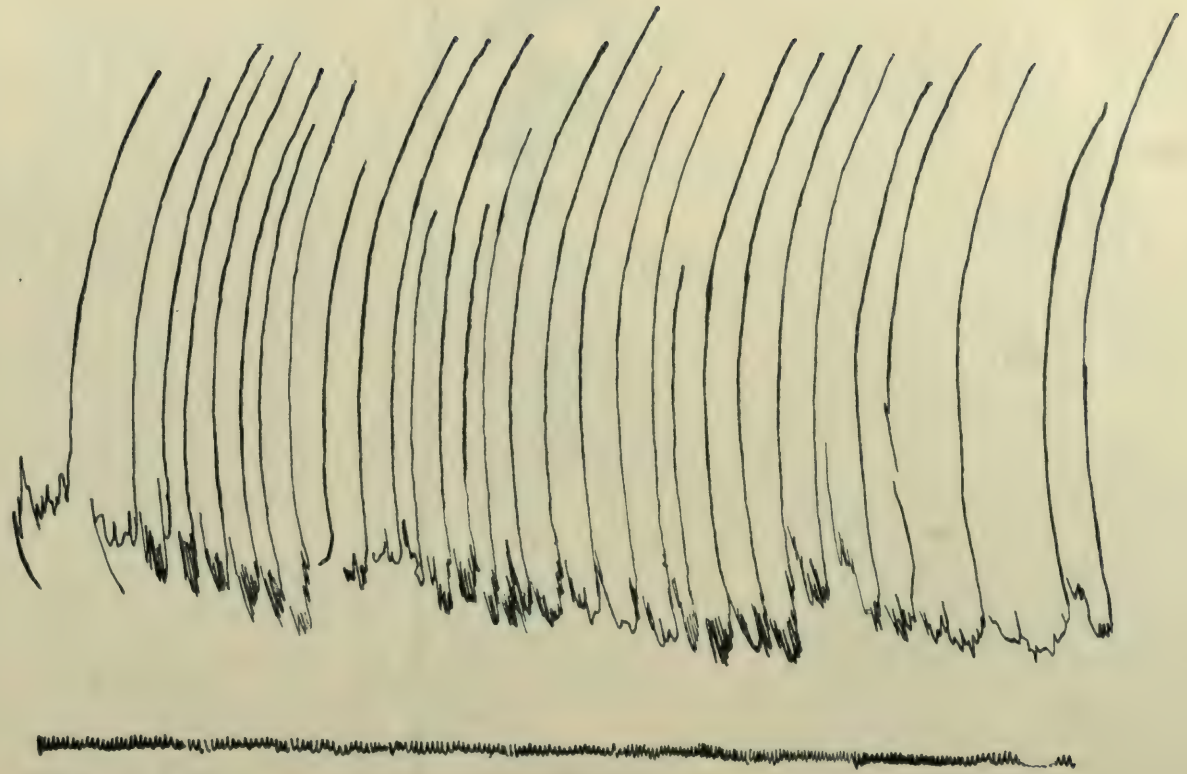


Fig. 4. — Case of vagotonia showing exaggerated, frequent and continuous hunger contractions; each hunger contraction is evidence of a rise in the intragastric pressure of 30 to 40 mm. Hg.

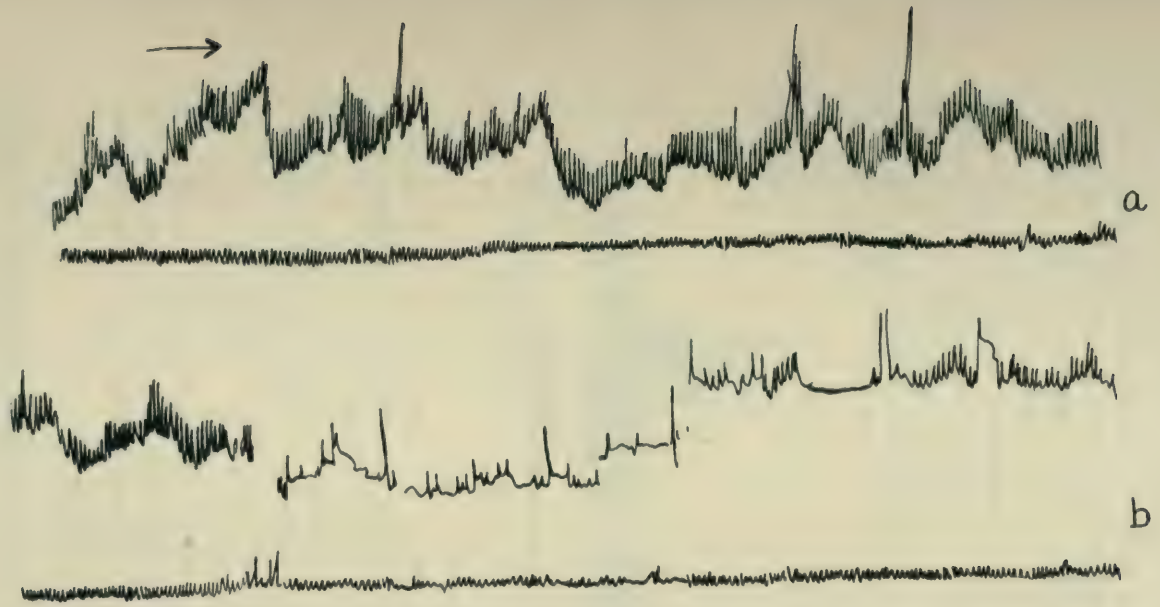


Fig. 5.—Tracing from a case of primary atony, showing progressive loss of tone (diminution and final disappearance of tonal waves). Duration of observation, one-half hour.

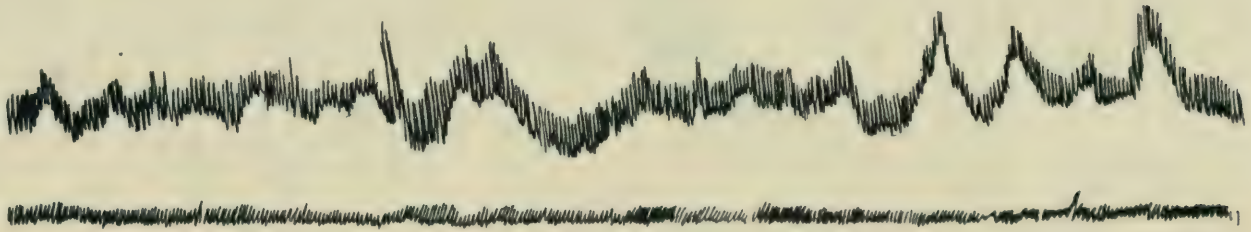


Fig. 6.—Tracing from case of ulcer (Type III) showing loss of normal hunger contractions; retention of tonal waves.

secretion, the constant presence of acid secretion in the fasting stomach inhibits the contractions, an appearance of atony being given.

Primary Atony.—This is evidenced by a diminution or disappearance of tonal contractions and a disappearance of hunger contractions. At the beginning of the observation moderate tonal contractions may appear, but these soon disappear and leave a curve which is characterized by absence of elevations and the maintenance of a continuous and unchanging level.

In cases of incompletely developed atony one occasionally may see small contractions or groups of moderate tonal waves, but the general curve as observed for the entire period is usually devoid of such demonstrations of tonus on the part of the gastric musculature.

Secondary atony accompanying organic lesions will be discussed under the appropriate headings.

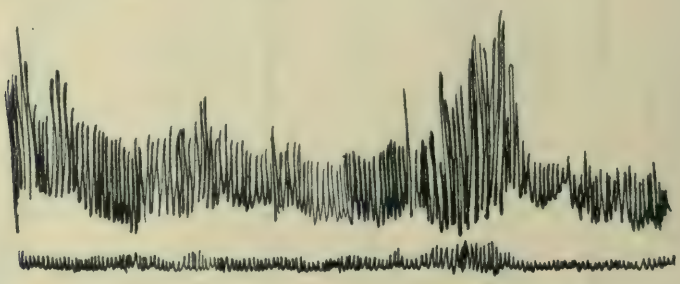


Fig. 7.—Atony secondary to callous ulcer on lesser curvature. Note complete absence of tonus and hunger waves.

We have not had an opportunity to study cases of pure gastritis. Catarrhal inflammations frequently complicate other anatomic lesions such as ulcer or carcinoma, and the descriptions of these conditions necessarily would include the effect of the catarrhal condition plus that of the main lesion. A case, however, has been reported in the literature[10] in which a gastritis was accompanied by a practically complete absence of motor activity.

Gastric and Duodenal Ulcer.[11]—No differentiating characteristics between these two types of ulcer could be demonstrated. It is of advantage to describe under different headings the tracings obtained.

1. Ulcer cases with practically normal tracings. These represent about one-fifth of the tracings.

2. Cases with retained tonal contractions, but irregular and isolated hunger contractions. These, too, represent about one-fifth of the cases.

10. Hamburger and Luckhardt: Jour. Am. Med. Assn., 1916, **66,** 1831.

11. This subject is described in detail by one of us in another article to be printed in the Annals of Surgery.

3. Ulcer cases, characterized by the disappearance of hunger contractions, but with retained tonus. These comprise also about one-fifth of the cases. Groups 2 and 3 together may be classed as those giving irregular tracings.

4. Cases of secondary atony. These are fewer in number. All gradations of this disturbance can be demonstrated. The presence of large, deeply punched out lesions in the body of the stomach has an inhibiting effect on the motor activity, and atonic conditions result. Pylorospasm is frequently associated with these large ulcers.

5. Cases of pyloric stenosis. In the early stages there is increased tonus and more prolonged and sustained hunger contractions. In the late stages a fatigue atony may appear. Between these two limits, all stages are observed.

Carcinoma Cases. — Here, too, the motility of the stomach may exhibit all changes from hyperactive conditions to marked degrees of atony. When the tumor is comparatively small, or when it is still limited to the superficial layers of the stomach wall, no disturbance is noticeable in the muscular activity. The tonus and hunger contractions are of normal volume and repeat themselves with the regularity customary to healthy stomachs. This is also true in the case of those tumors in the body of the stomach which may or may not be large in extent, but which are limited practically to the mucous membrane.

Tumors near the pyloric sphincter may be differentiated in accordance with the production or absence of a stenosis. In those cases with malignant stenosis, the same facts were observed as with the benign stenosis.

Carcinomata of the stomach are usually accompanied by various degrees of chronic gastritis, and in many cases the latter assumes a dominant position in regard to the disturbances of function and causes a practical disappearance of all muscular activity.

Tabes with Gastric Crises.—One such case has been studied, the observation being made during the intervals between attacks. The curve is one of complete incoordination, periods of marked overactivity following periods of atony with an absence of the normal rhythm. All of these phases were visible during a comparatively short period of observation.

DISCUSSION

The smooth muscle wall of the stomach is arranged in three layers and accomplishes a predominating churning motion in the fundus of the stomach and a predominating propulsive exertion in the antrum. In addition, there is provided a valve at both the entrance to, and the exit from, the stomach. Inasmuch as the natural tonicity of smooth

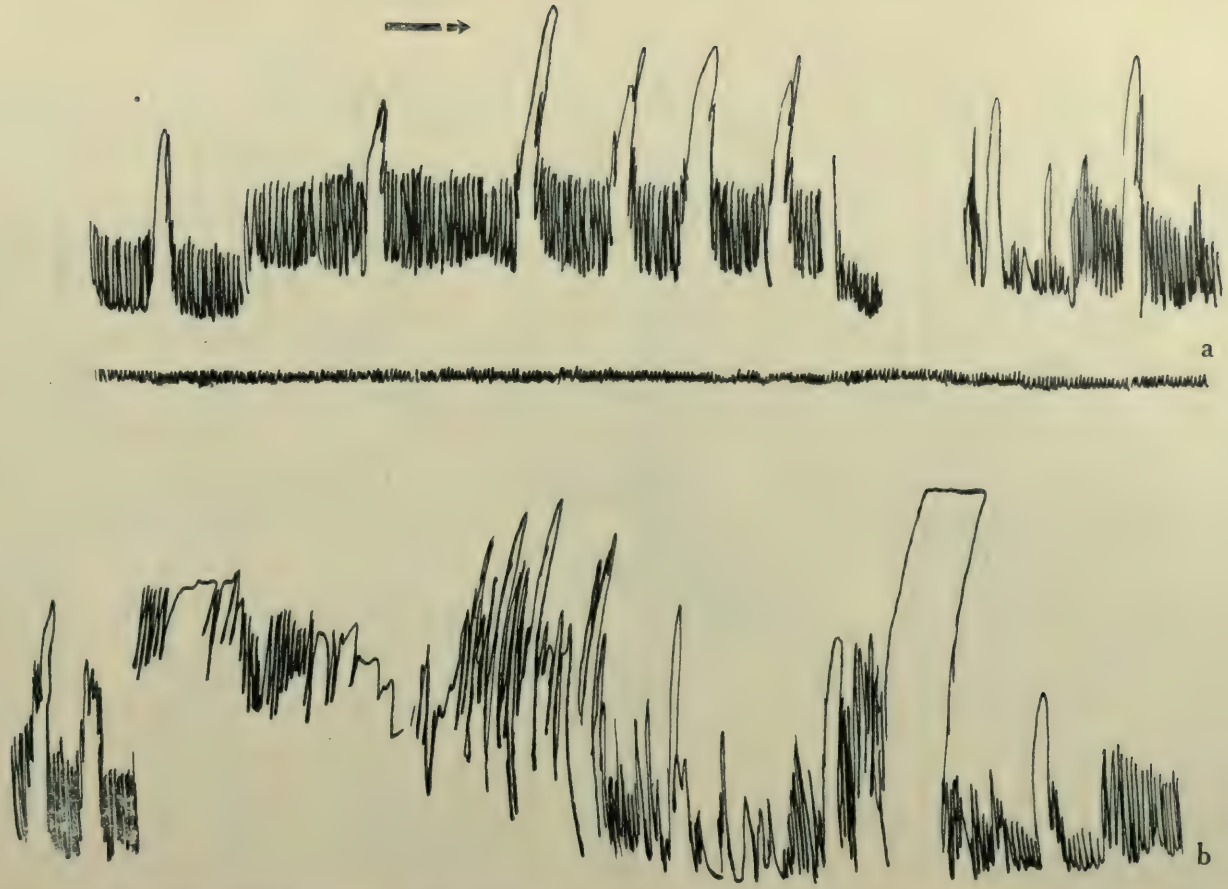


Fig. 8.—Benign pyloric stenosis. The hunger contractions are broader, more sustained and frequent. The middle tracing is the control.

muscle fiber is always in evidence, it follows that the entire structure is constantly in a state of contraction on its contents. The presence of valve formations at both ends of the stomach establishes conditions for intragastric pressures which would naturally vary with the activity of the organ.

This variation in the natural tension of the muscle fiber produces what has been called by Cannon and Carlson the "tonus contractions" of the stomach. In a healthy organ these tonal variations are repeated regularly and rhythmically three to four times each minute, and establish an intragastric pressure of an average moderate degree.

It has been conclusively shown in purely physiologic work that the appearance of any active contraction of the stomach is dependent on a normal tonus of the musculature, and has its origin in an increase in the intragastric pressure.

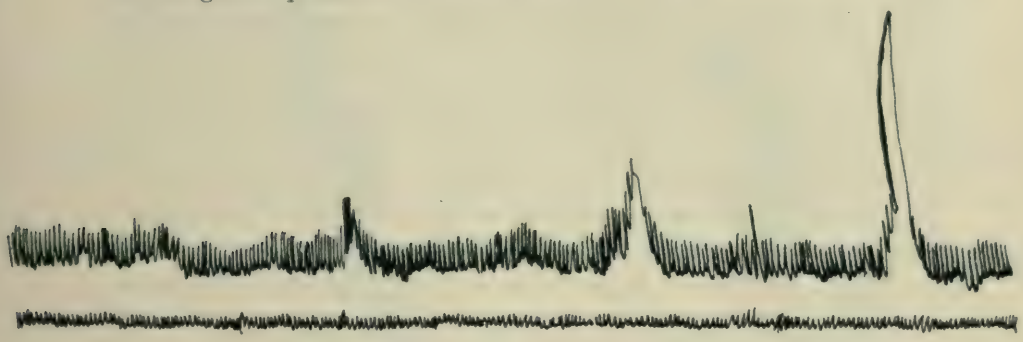


Fig. 9.—Same case as illustrated in Figure 8, taken six months later. Note that the tracing is now one of secondary atony, such as accompanies ectasia.

Tonus Contractions. — The tonus contractions which the kymographic drum records originate in the gastric musculature. Both Ducchessi and, more recently, Alvarez[11a] demonstrated like contractions of a spontaneous nature in excised portions of the stomach wall, the three portions of the viscus (cardia, fundus and antrum) each exhibiting a characteristic type of movement. With our technic, the introduction and inflation of the balloon, by raising intragastric pressure, gives rise to these typical tonus contractions, as explained by Cannon. That the contractions can arise either from the fundus or the antral portions, was clearly proved by Sick, who obtained contractions from both ends in the same person, the fundus contractions being weaker and of less amplitude than the antral. It is probable, however, that in the cases examined by us, the balloon, which, even when inflated, is only the size of a medium large lemon, moves easily in the stomach.

11a. Alvarez, W. C.: Jour. Am. Med. Assn., 1915, **65,** 388; ibid., Am. Jour. Physiol., 1916, **41,** 321; 1916, **40,** 358; 1917, **42,** 422.

and is soon pushed down by the contractions to the antral region, where the larger hunger contractions are produced. Rogers and Hardt,[12] by enclosing a smaller balloon filled with bismuth within a larger inflatable balloon, demonstrated vigorous contractions at the fundus, sweeping down over the antrum. Alvarez[13] found the cardia and lesser curvature to be the most irritable portion of the stomach. Keith[14] suggested the presence of a rate-making node on the lesser curvature near the cardia.

The tonus contractions appear in all stomachs approaching the normal or acting in an efficient physiologic manner. They are diminished or absent in the following conditions:

Gastric Atony.—This refers to the simple atony often seen as part of the picture of a gastric neurosis, or to the atony secondary to pulmonary tuberculosis, secretory disturbances of the stomach, etc. The atony here may appear only after the lapse of ten to fifteen minutes of observation, or after the primary contractions incident to the introduction of a foreign body have subsided. In such an instance the atony is progressive. In tonic stomachs there may be inhibition at first, but soon the tonus contractions appear and are thereafter steadily maintained throughout the observation. In a tonic stomach the amplitude and rate of contraction are usually constant; in cases with disturbed tone, the contractions are irregular, unequal, and the rate often variable.

Atony Secondary to Operation on the Stomach.—This subject has been more fully described in a recent paper by the authors.[15] Suffice it to say that a pre-operative state of atony may continue after operation, particularly after gastro-enterostomy. The conclusions of the former paper were noted many years ago by Ducchessi[16] and Denechau.[17]

The recovery of tone in the cases benefited by operation is progressive and is strikingly illustrated by our curves.

Ectatic Atony, or Atony Secondary to Pyloric Obstruction.—Such an atony appears as a late stage of mechanical pyloric obstruction, or is secondary to the pylorospasm of ulcer, distant from the pylorus. It is of marked degree and is the most complete of any observed.

Increased tonus is observed less frequently than diminished tonus; it is seen in irritative conditions of the vagus, as part of the pitcure in

12. Rogers and Hardt: Am. Jour. Physiol., 1915, **38,** 274.
13. Alvarez, W. C.: Am. Jour. Physiol., 1916, **40,** 585.
14. Keith: Quoted from Alvarez; see Footnote 13.
15. Wilenksy and Crohn: Am. Jour. Med. Sc., 1917, to be published.
16. After grave lesions the curve of tonicity remains constantly depressed and the wave of contraction is distinctly periodic. ("Après des graves lésions, la ligne de tonicité se maintient constamment très déprimé et la fonction motrice est nettement périodique." Arch. ital de biol., 1897, **27,** 61.)
17. Denechau: Paris Thesis, 1907.

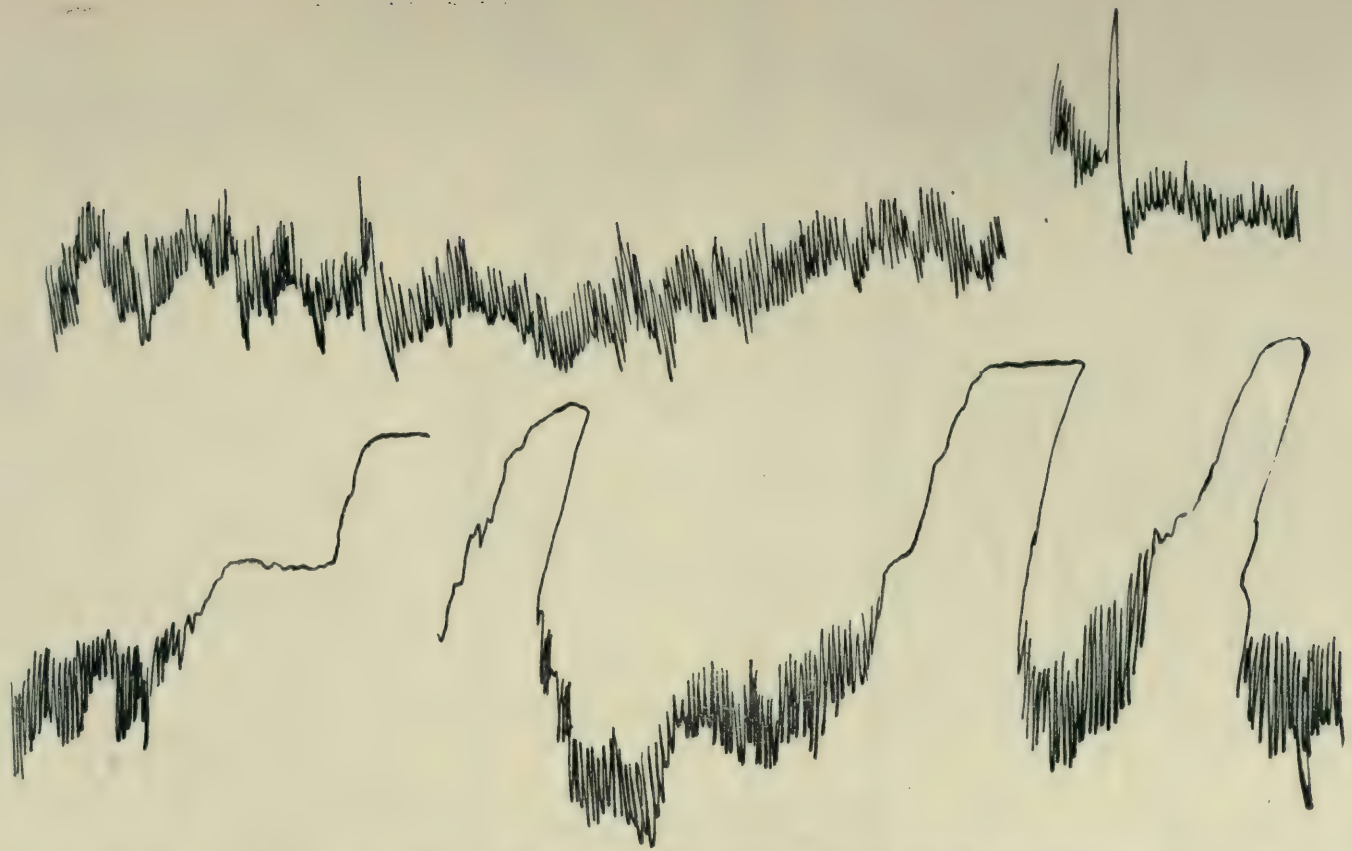


Fig. 10.—Malignant pyloric obstruction. Many of the hunger contractions are sustained and represent tetanic contractions of the empty viscus. (Control curve not given.)

tabes with gastric crises, and in the early stages of mechanical pyloric obstruction. In a case of carcinoma ventriculi, with infiltration of the mucosa with neoplastic tissue, increased tonus was observed, though no pyloric involvement occurred. This was due to rigidity of the wall of the viscus as well as to actual diminution of the interior space of the organ, the stomach assuming the appearance radiographically typical of a "leather-bottle" stomach.

Hunger Contractions.—In discussing the appearance of hunger contractions on our kymographic records, while we must agree with both Cannon and Carlson that hunger contractions are evidence of normality in the stomach, yet exceptions do occur, for we have observed the maintenance of good hunger contractions in cases in which gastric or duodenal ulcer was demonstrated at operation. Exceptions occur, however, in a small number of instances; as a rule, patients from whom a tracing has been obtained in which good and frequent hunger contractions occur, have proved at exploratory operation to be devoid of an organic lesion.[18]

The hunger contractions do not usually appear for the first few minutes of the observation, but once established, they follow each other in regular rhythm, separated by an interval which varies in each person, being in some ten to fifteen seconds; in others as long as sixty seconds apart. Sporadic or isolated contractions are less significant. The height of the contraction also varies, depending on the tonicity of the organ, being from 10 to 30 or 40 mm. Hg. Contractions of the nature of hunger contractions, of less than 10 mm. Hg. are really to be regarded as slightly exaggerated tonus waves, and represent the transition between tonus and hunger contractions.

Absence of hunger contractions is noted in atony, primary or secondary, and in organic lesions of the stomach and duodenum, particularly in ulcer. Carlson[19] observed diminution of tonic contractions in dogs in which the vagi had been severed.

Exaggeration of hunger contractions has been noted in conditions of vagus excitation. May[20] noted contractions three times the normal height on stimulating the vagus.

In pyloric stenosis we have noted that the nature of the contraction may be changed so that the summit of the contraction curve instead of being sharp or accuminate, with the fall of pressure sudden and immediately following the fastigium, is rounded or sustained as a plateau. Such a sustained elevation may endure for one, two or three minutes and represents a tonic spasm or tetany of the gastric musculature. It

18. Wilensky and Crohn: Tr. Am. Gastro-Enterol. Assn., 1916.
19. Carlson, A. J.: Am. Jour. Physiol., 1913 **32.**
20. May: Jour. Physiol., 1904, **31,** 260.

is pathognomonic, and was observed in two cases in which visible abdominal peristalsis was also evident. A similar condition was observed by Sick[7] and by Carlson and Ginsburg[21] in children with mechanical obstruction at the outlet of the viscus.

The case of tabes with gastric crises represents all phases of tonus from atony to hypertonicity, but is characterized by a complete absence of uniformity and by the occurrence of constant and unsystematized variations. The stomach seems to be in the same condition of ataxia as are the extremities, the bladder and the rectum.

A comparison between our interpretation of the kymographic tracings and the results of the Roentgen-ray examinations shows a fair degree of similarity. The most striking point is that good tonus con-

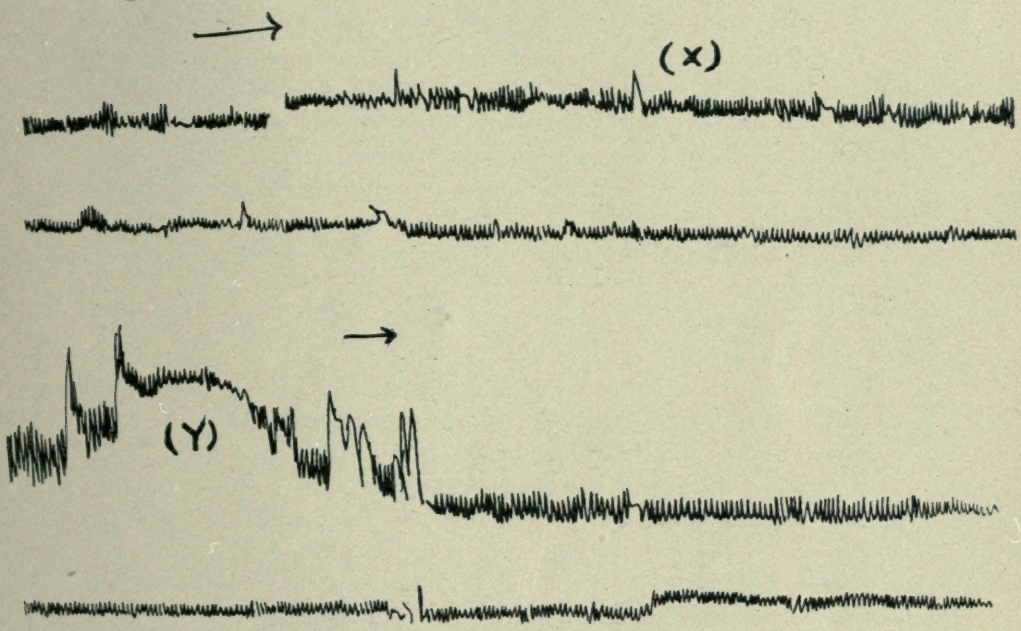


Fig. 11.—Tracing from a case of tabes with gastric crises. All phases are seen, from complete atony in the first few minutes to hyperatony, and even a sustained tetanic contraction as observed at (Y). The latter is often immediately followed by a long period of atony. Duration of observation, one-half hour.

tractions on the tracings signify good motility and normal emptying time of the stomach. No relationship exists between the tonus and hunger contractions demonstrated in the kymographic tracings, and the digestive peristalsis seen under the fluoroscope. As a rule, the tone of the stomach in the fasting state gives no indication of the degree of activity during digestion, and a state of atony in the fasting stomach

21. Carlson and Ginsburg: Am. Jour. Physiol., 1915, **39**, 310.

may, under the stimulus of active digestion (barium-zoolak mixture), give place to fair, or active, or even hyperactive peristalsis. On the other hand, a complete absence of tonus contractions in one of the cases studies, corresponded with a complete absence of digestive peristalsis as seen under the fluoroscopic screen.

It has become evident from the data which we have collected to date, that hunger contractions and digestive peristaltic contractions are not identical. In fact, in Boldyreff's[8] experimental studies on dogs, a disappearance of hunger contractions after the introduction of food into the stomach was clearly demonstrated.

SUMMARY

We may summarize our findings under the following captions:

1. The human fasting stomach, into which has been introduced an inflated balloon connected at its distal end with a registering tambour, gives, normally, evidence of periodic variations of tone, at the usual rate of three to four waves per minute. Hunger contractions of greater amplitude, and caused by more rapid increases in intragastric pressure, occur singly or in groups.

2. The appearance of these two types of waves characterizes a normal stomach.

3. No disturbance was noted in purely secretory or other functional gastric disturbances.

4. The occurrence of atony of the stomach, both primary and secondary, is marked by the disappearance of hunger contractions, and when advanced, also of the tonal waves.

5. Organic disease of the stomach, including ulcer and carcinoma, disturbs the motor function of the stomach, frequently causing a disappearance of the normally existing hunger contractions. In gastric or duodenal ulcer the normal tonal variations may be maintained, but usually are disturbed, one or both elements disappearing.

6. In pyloric stenosis, either benign or malignant, the tonus is at first markedly increased, the occurrence of gastric tetanic contractions often being observed. As the stenosis progresses, the features of secondary atony of the gastric musculature may supervene.

7. Tabes, with gastric crises, gives evidence of complete incoordination of the neuromuscular control of the organ.

8. There is little or no correspondence between the tonal and the hunger contractions of the fasting stomach and the digestive peristalsis of the viscus after a meal.

9. The method utilized in these experiments is a physiologic one, well adapted to a study of the variations in the functional capacity of the gastric musculature in health and disease. It is not, primarily, a means for diagnosis.

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